Congestive Heart Failure: Turning Failure Into Success

Wednesday, Feb 21, 2018

Welcome & Opening Remarks

Robert T. Smith, MD, FACP

Introduction of Conference Theme & Speaker

Brian Schwartz, MD, FACP, FACC, FSCAI

Kettering Heart and Vascular Medical Director

Keynote Speaker

Javed Butler, MD, PhD

Heart Failure 2018: Where Are We and Where Are We Going!

Evolution to HFpEF

Q&A With Dr. Butler

Robert T. Smith, MD, FACP

Break, Vendor Fair, and Refreshments

Understanding HFrEF/Advanced HF

Deepthi Mosali, MD, FACC

KETTERING Health Network

HEART & VASCULAR CARE

Mechanisms of HFrEF

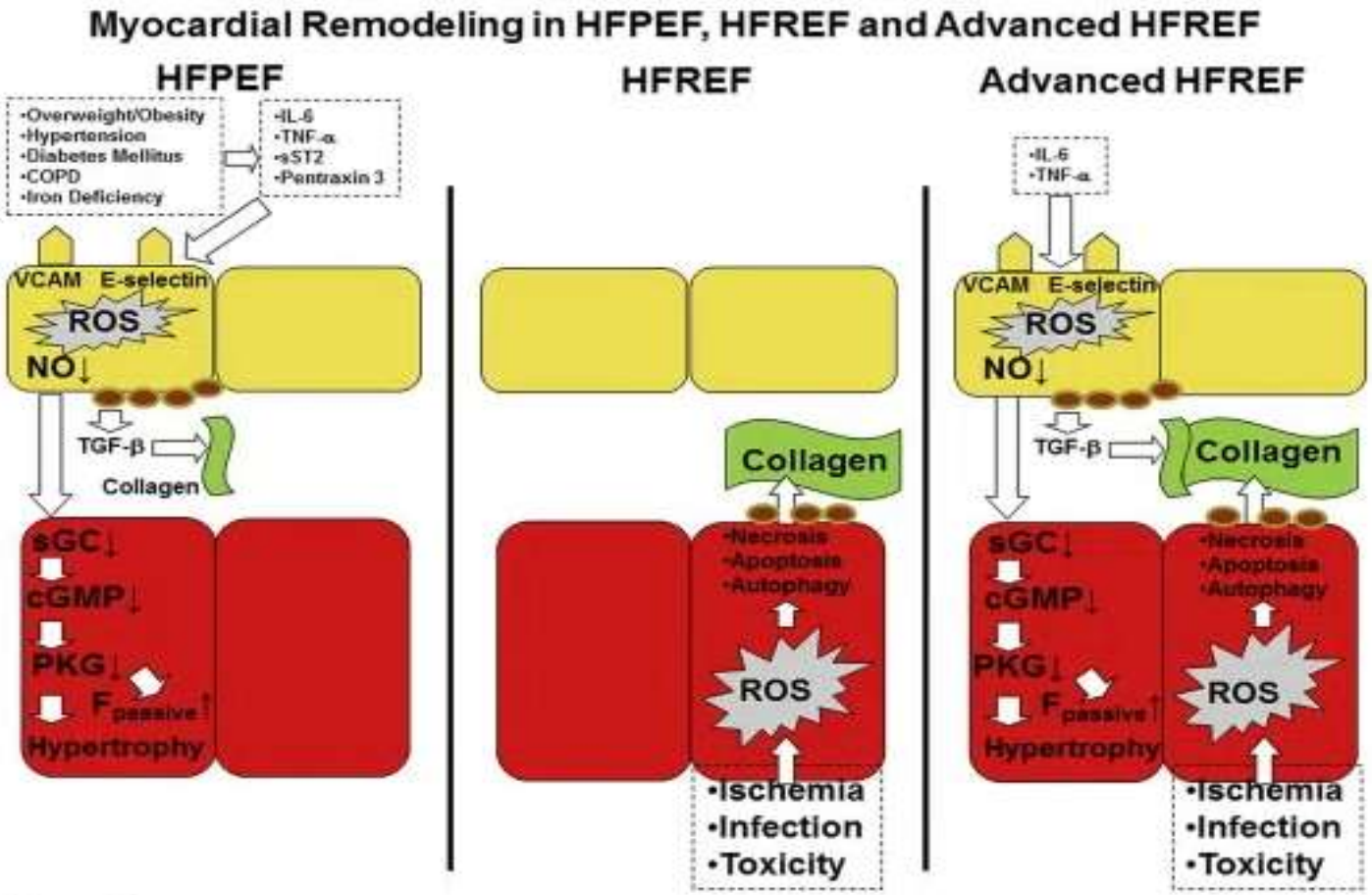
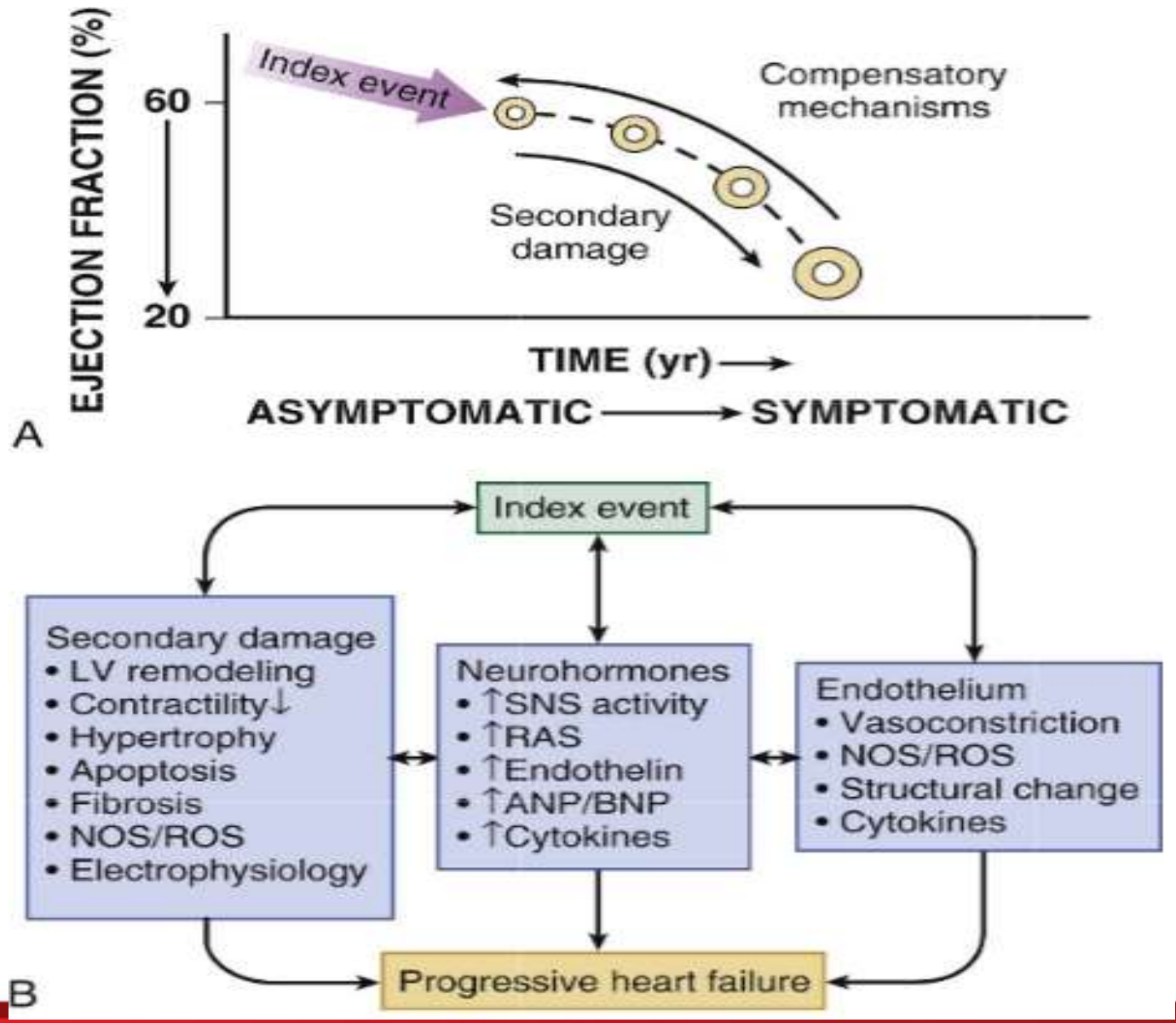


Figure 3

Myocardial Dysfunction and Remodeling in HFPEF, HFREF, and Advanced HFREF

In HFPEF, myocardial dysfunction and remodeling are driven by endothelial oxidative stress. In HFREF, oxidative stress originates in the cardiomyocytes. In advanced HFREF, both mechanisms get superimposed. Abbreviations as in Figures 1 and 2 .


EJECTION FRACTION (%)
60
20
Index event
Compensatory mechanisms
Secondary damage
TIME (yr)
ASYMPTOMATIC
SYMPTOMATIC
A
Index event
Secondary damage
• LV remodeling
• Contractility↓
• Hypertrophy
• Apoptosis
• Fibrosis
• NOS/ROS
• Electrophysiology
Neurohormones
• ↑SNS activity
• ↑RAS
• ↑Endothelin
• ↑ANP/BNP
• ↑Cytokines
Endothelium
• Vasoconstriction
• NOS/ROS
• Structural change
• Cytokines
Progressive heart failure
B

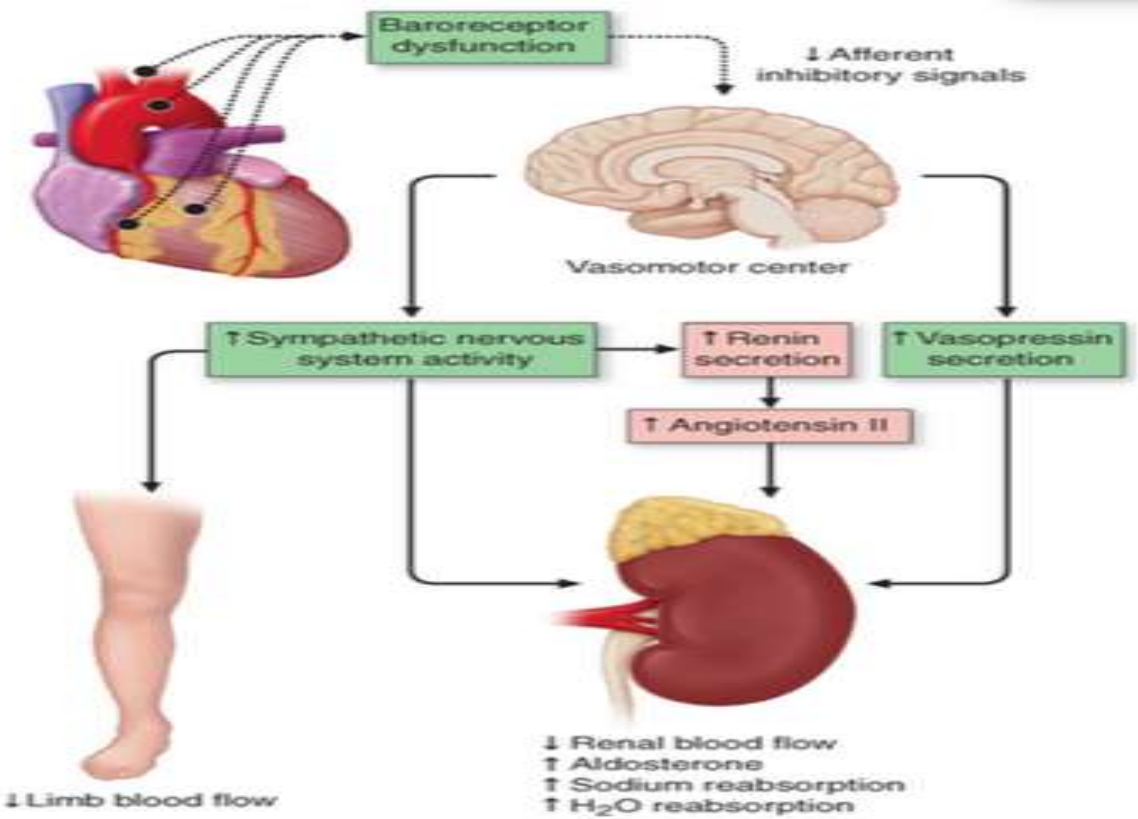
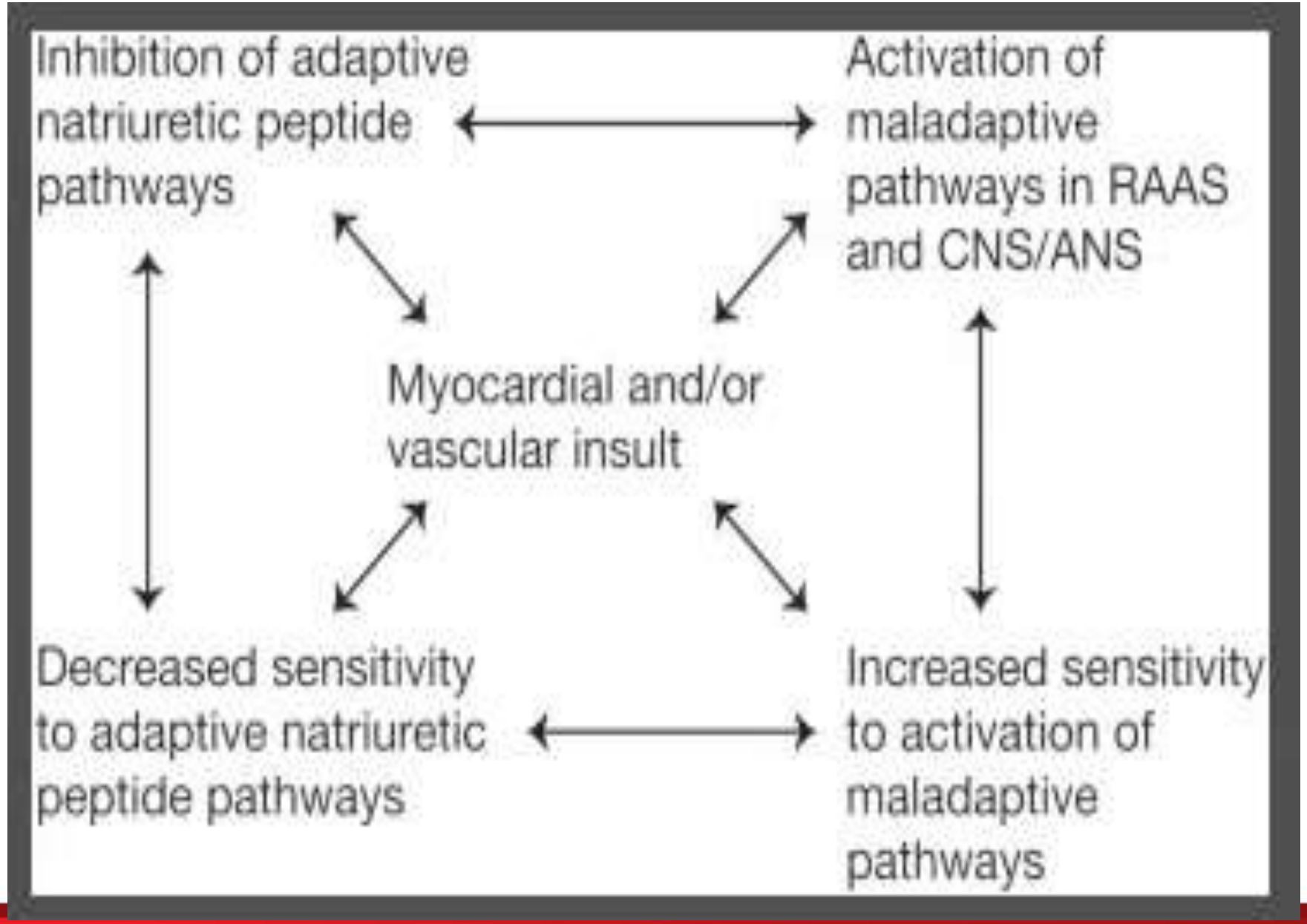
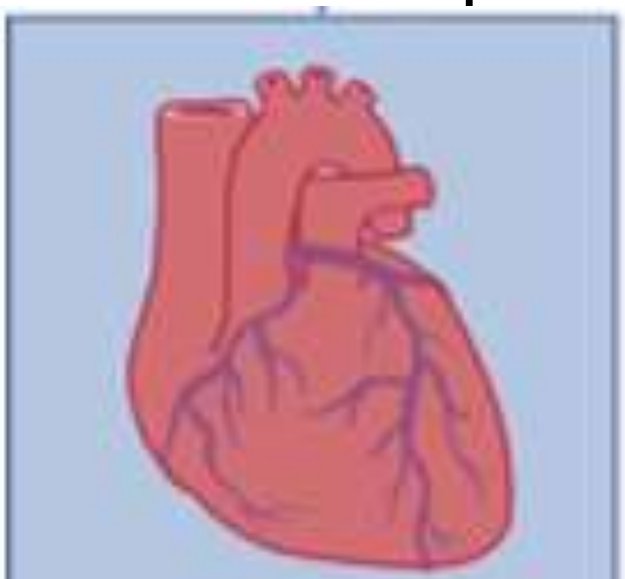


Figure 1. Activation of neurohormonal systems in heart failure
Decreased cardiac output in patients with heart failure with reduced EF results in the unloading of high-pressure baroceptors (black circles) in the left ventricle, carotid sinus, and aortic arch. This unloading leads to generation of afferent signals to the central nervous system (CNS) that, in turn, lead to activation of efferent sympathetic nervous system pathways that innervate the heart, kidney, peripheral vasculature, and skeletal muscles. This unloading also leads to afferent signals to the CNS that stimulate cardioregulatory centers in the brain that stimulate the release of arginine vasopression from the posterior pituitary.


Inhibition of adaptive natriuretic peptide pathways
Activation of maladaptive pathways in RAAS and CNS/ANS
Myocardial and/or vascular insult
Decreased sensitivity to adaptive natriuretic peptide pathways
Increased sensitivity to activation of maladaptive pathways

Effects of persistent SNS activation

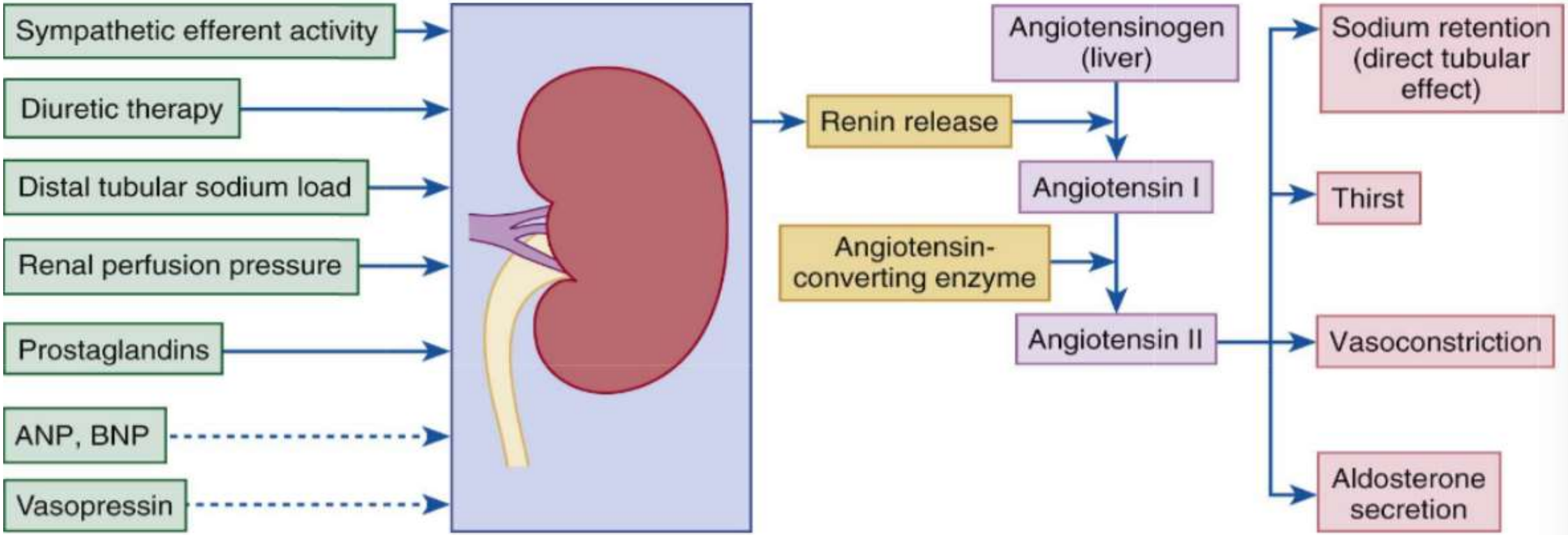


↓β-AR responsiveness
Myocyte hypertrophy
Myocyte necrosis
and apoptosis, fibrosis
↓Norepinephrine stores
↓Sympathetic innervation

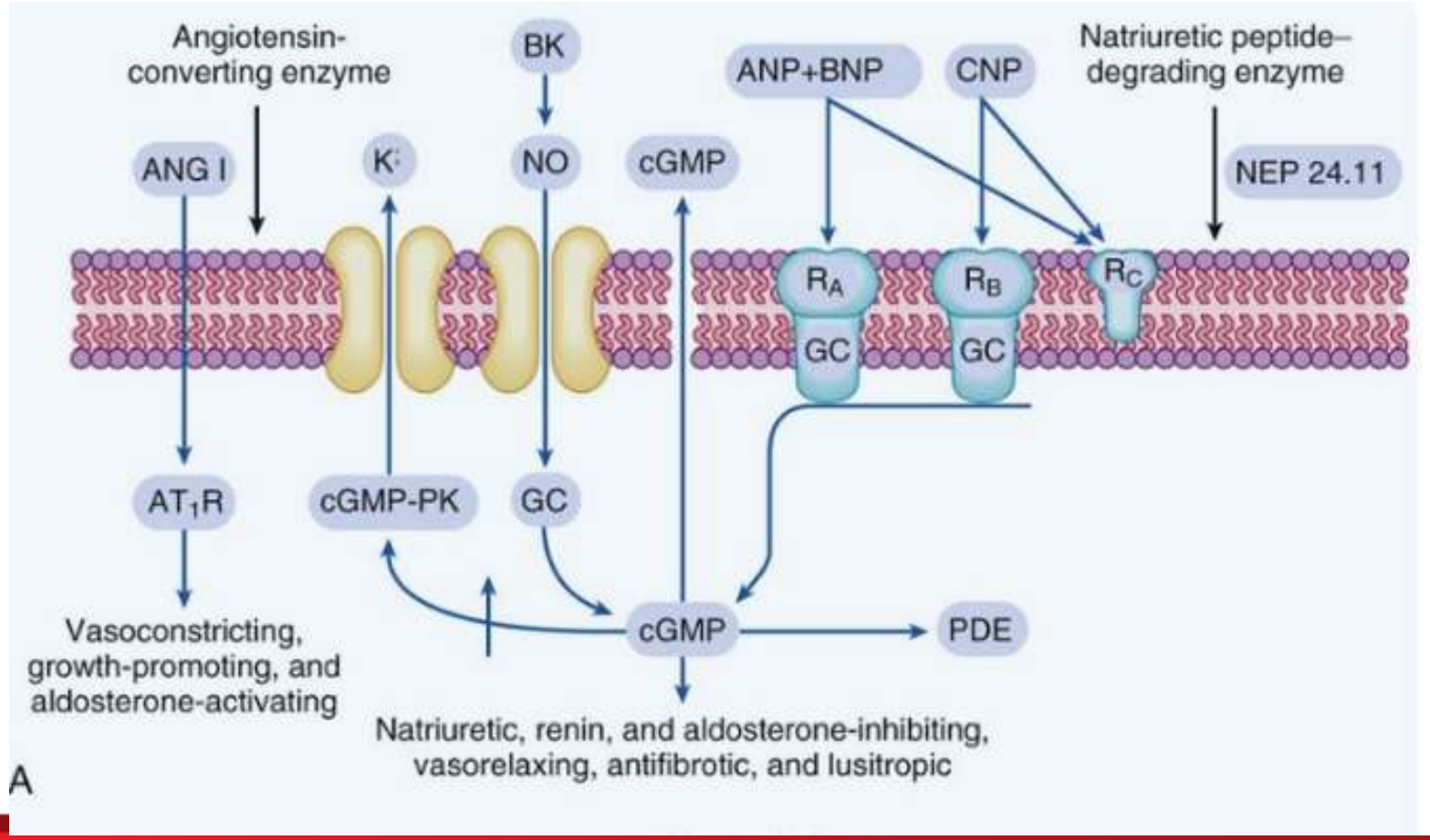
↑Tubular reabsorption of Na^+
Activation of RAS
↑Renal vascular resistance
↓Response to natriuretic factors
↑Renin release

Neurogenic vacoconstriction
Vascular hypertrophy

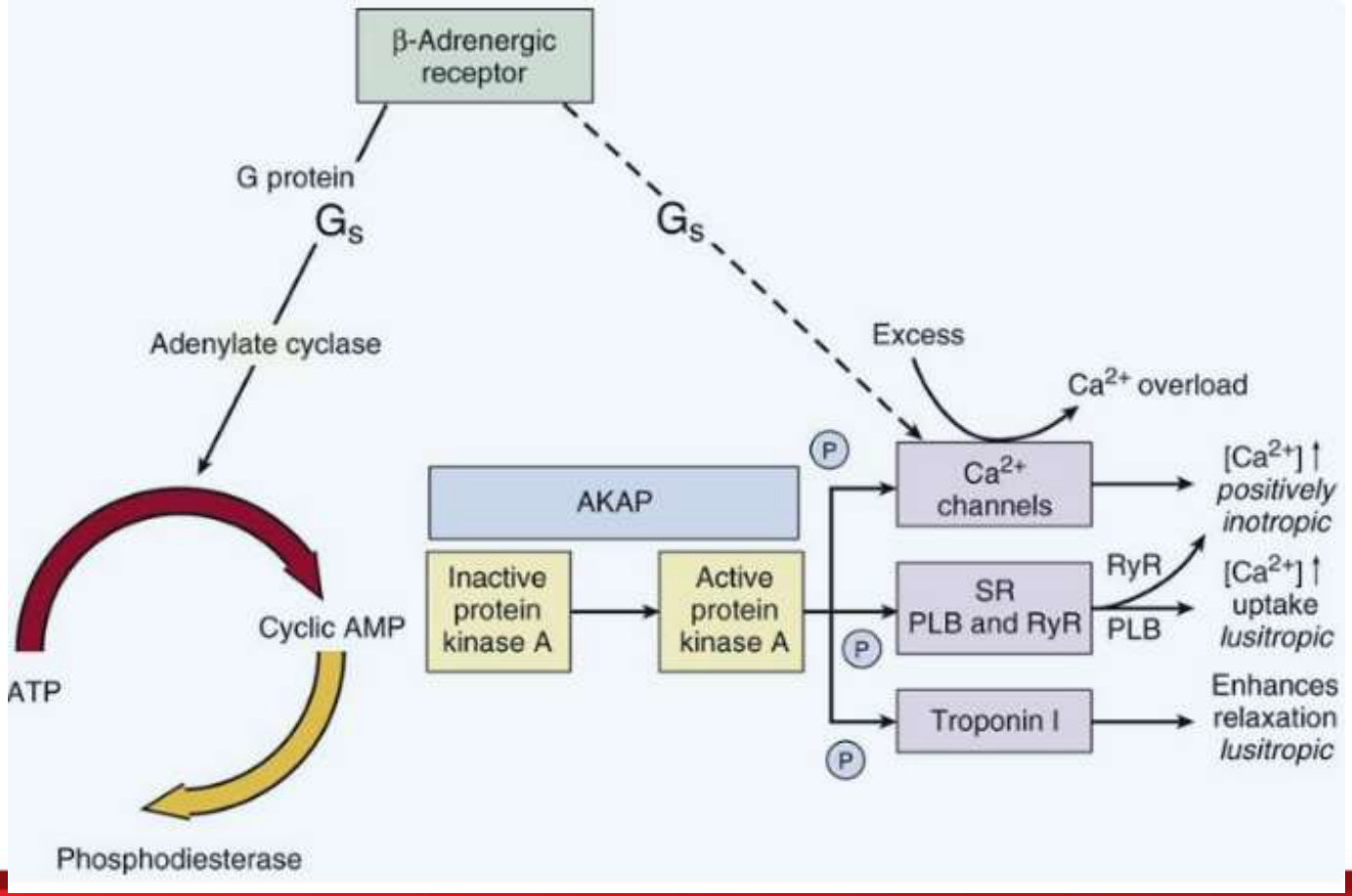
RAAS System activation



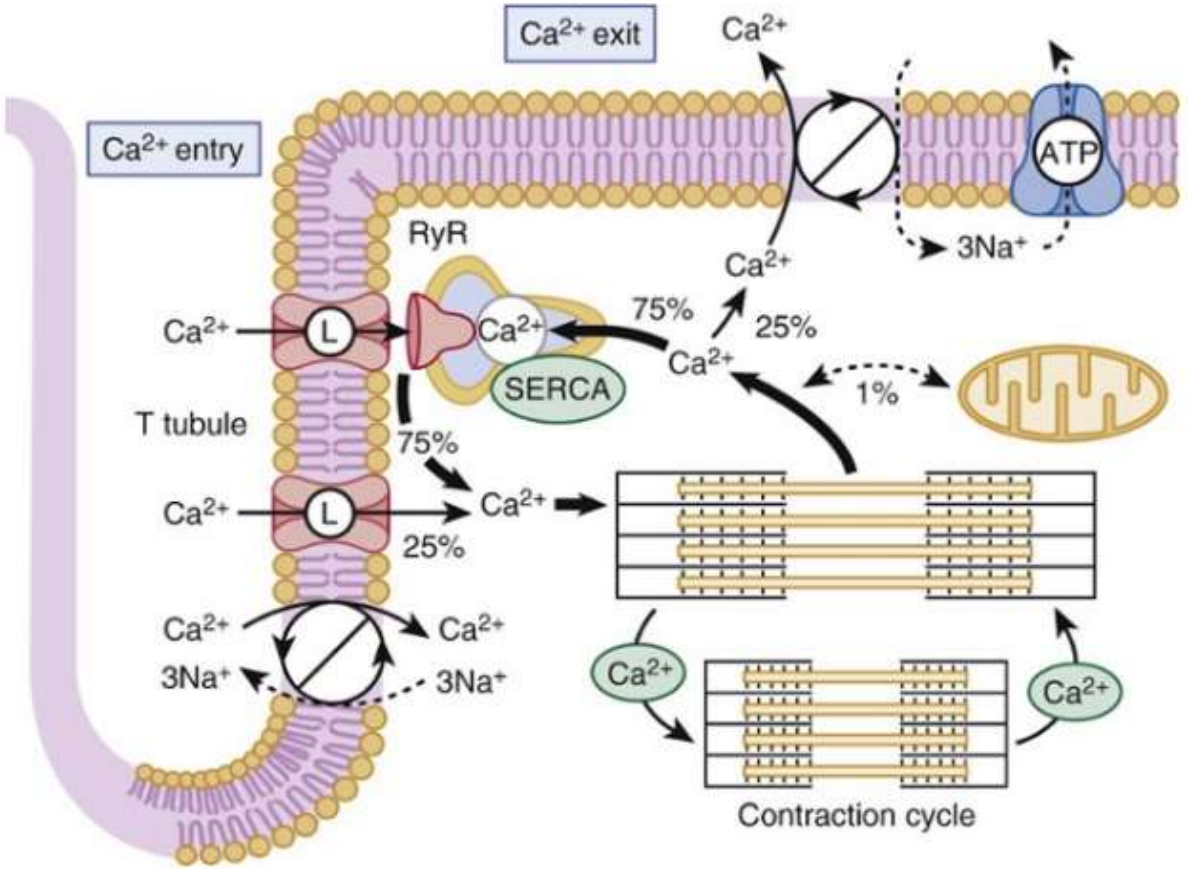
Natriuretic Peptides



Beta-Adrenergic signaling



Excitation-Contraction coupling



	ALPHA$_1$ MEDIATED	BETA MEDIATED
Electrophysiologic effects	±	++ Conduction Pacemaker **Heart** rate – AP duration
Myocardial mechanics	±	++ Contractility, lusitropy Stroke volume Cardiac output
Myocardial metabolism	± Glycolysis	++ O_2 uptake ↑ ATP
Signal systems	GPCR, can activate PKC and MAPK	GPCR, activates cAMP and PKA
Coronary arterioles	++ Constriction	+ Direct dilation +++ Indirect dilation (metabolic)
Peripheral arterioles	+++ Constriction SVR ↑ SBP ↑	+ Dilation SVR ↓ SBP ↓

AP = action potential; SBP = systolic blood pressure; SVR = systemic vascular resistance.

Changes in the biology of the failing heart

PROTEIN	CHANGE IN HUMAN HEART FAILURE
Plasma Membrane	
L-type calcium channels	Decreased*†
Sodium/calcium exchanger	Increased*†
Sodium pump	Reexpression of fetal isoforms
$Beta_1$-adrenergic receptor	Decreased*†
$Beta_2$-adrenergic receptor	Increased*
$Alpha_1$-adrenergic receptor	Increased*
Contractile Proteins	
Myosin heavy chain (MYHC)	Reversion to fetal isofom (↓MYHC6:MYHC7)
Myosin light chain (MYLC)	Reversion to fetal isoform
Actin	Normal*
Titin	Isoform switch (↑N2BA:N2B), hypophosphorylated
Troponin I	Normal*, hypo- and hyperphosphorylated‡
Troponin T	Isoform switch, hyperphosphorylated‡
Troponin C	Normal*
Tropomyosin	Normal*
Sarcoplasmic Reticulum	
SERCA2A	Decreased*†
Phospholamban	Hypophosphorylated
Ryanodine receptor	Hyperposphorylated†
Calsequestrin	Normal*
Calreticulin	Normal*

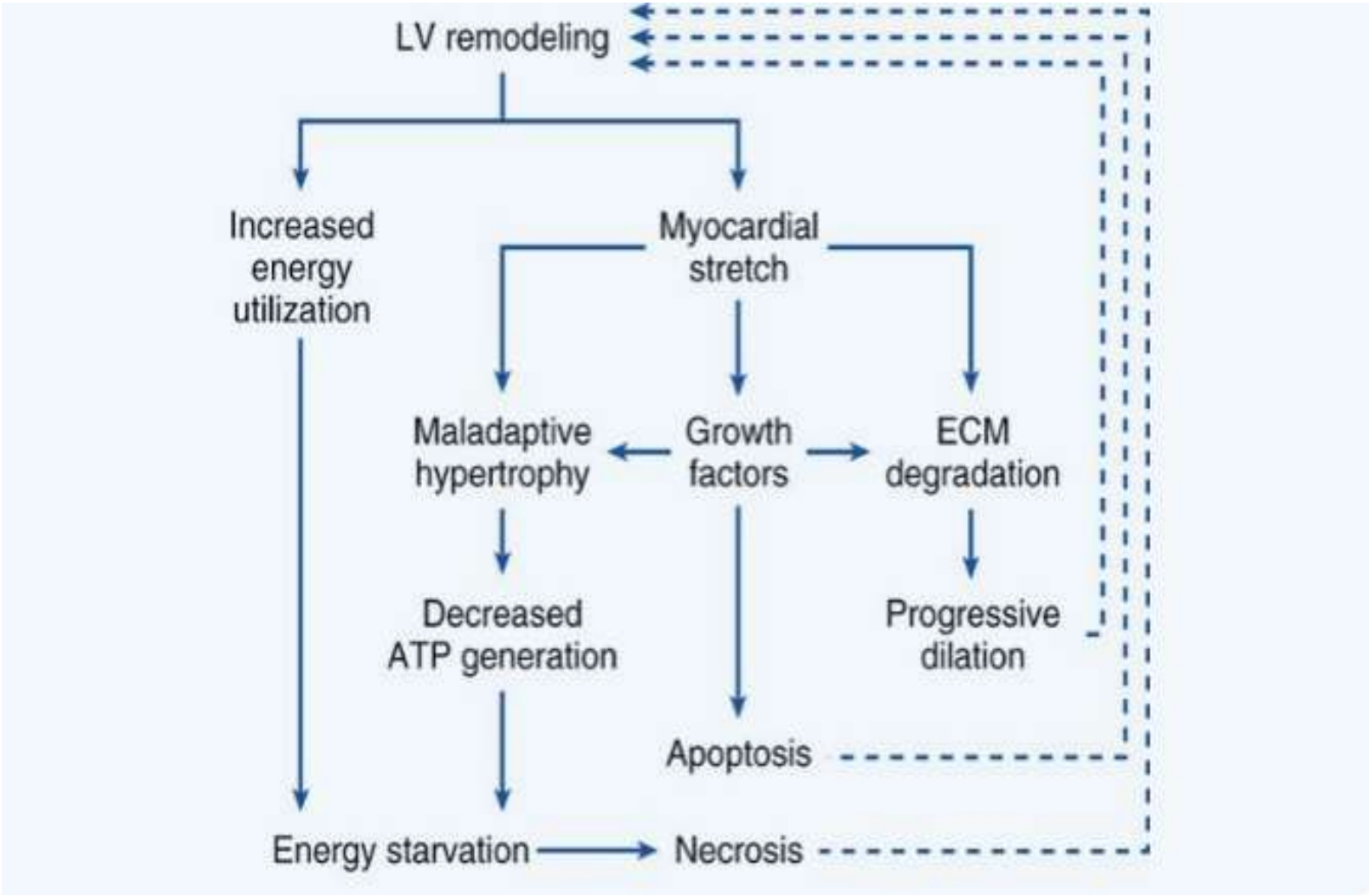

LV remodeling
Increased energy utilization
Myocardial stretch
Maladaptive hypertrophy
Growth factors
ECM degradation
Decreased ATP generation
Progressive dilation
Apoptosis
Energy starvation
Necrosis

TABLE e22-2 Mechanical Disadvantages Created by Left Ventricular Remodelin

Increased wall stress (afterload)
Afterload mismatch
Episodic subendocardial hypoperfusion
Increased oxygen utilization
Functional mitral regurgitation
Worsening hemodynamic overloading
A stretch-induced activation of maladaptive signal transduction pathways
Stretch-induced activation of maladaptive gene programs

TABLE e22-2 Mechanical Disadvantages Created by Left Ventricular Remodelin

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Stretch-induced activation of maladaptive gene programs
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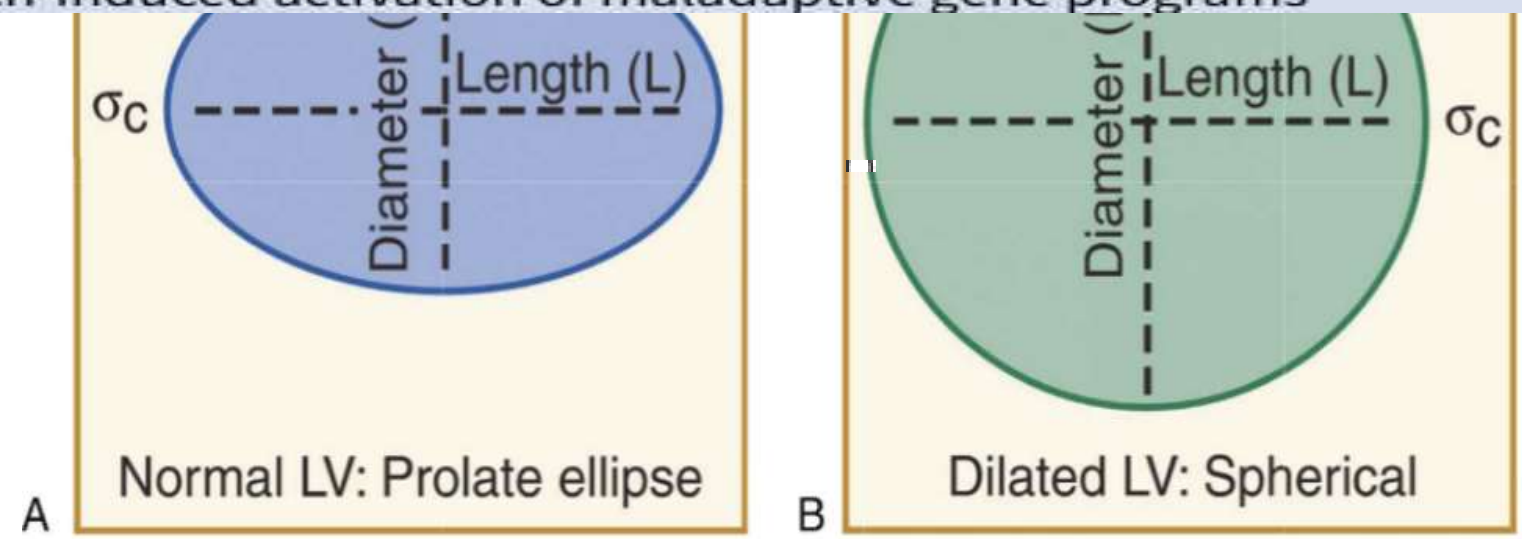
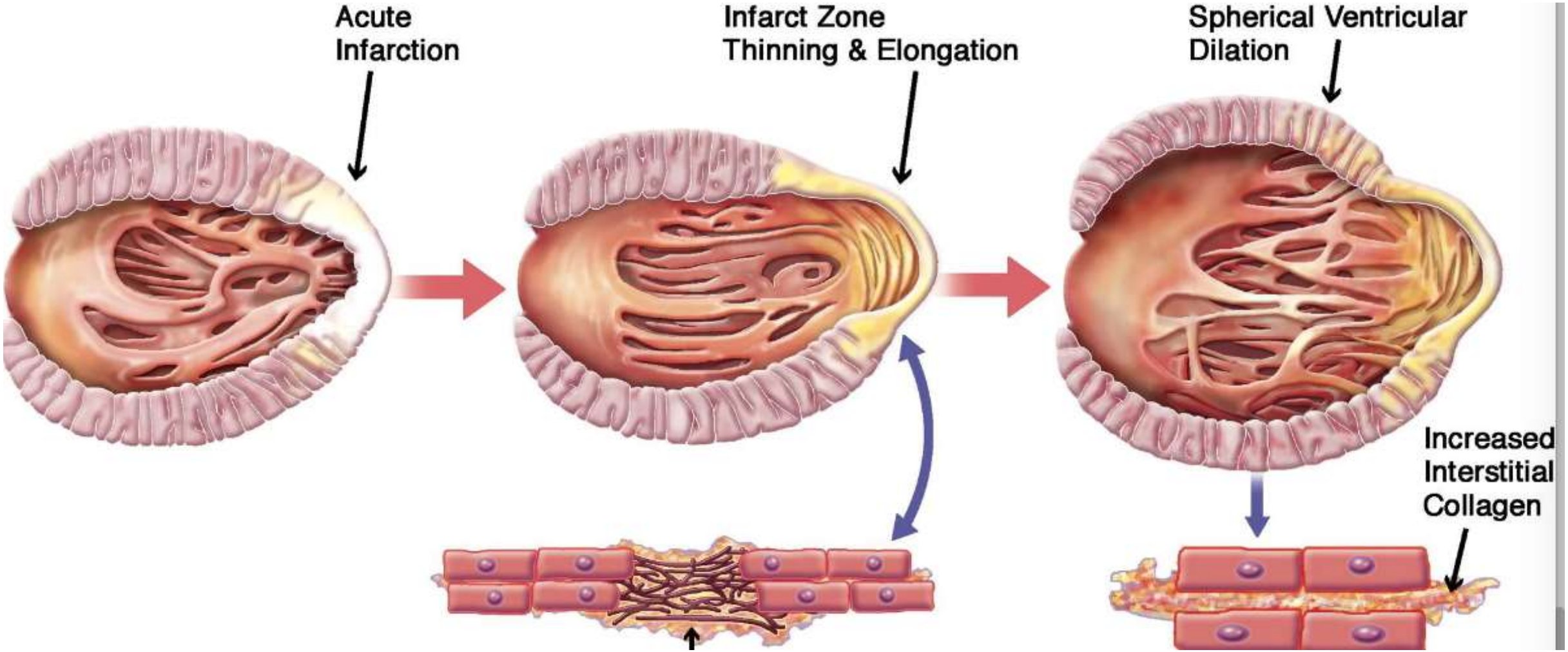



Acute
Infarction
Infarct Zone
Thinning & Elongation
Spherical Ventricular
Dilation
Increased
Interstitial
Collagen

Box 1

Myocardial changes in LV remodelling

Alterations in myocyte biology

Hypertrophy

Myosin heavy chain (fetal) gene expression

Myocytolysis

Changes in cytoskeletal proteins

β-Adrenergic desensitization

Excitation–contraction coupling

Myocardial changes

Myocyte loss

- Necrosis
- Apoptosis
- Autophagy

Alterations in the extracellular matrix

- Matrix degradation
- Myocardial fibrosis

Alterations in LV chamber geometry

Increased size

Increased sphericity

Wall thinning

Mitral valve incompetence

LV, left ventricular.

Key points

Heart failure with reduced ejection fraction (HFrEF) is initiated when an 'index event' causes the pumping capacity of the heart to be impaired

Reduced pumping capacity of the heart results in compensatory activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, which together are referred to as 'neurohormonal activation'

Neurohormonal activation results in a series of coordinated responses that collectively work to restore cardiovascular homeostasis in the short-term

Sustained neurohormonal activation drives the progression of HFrEF through the deleterious effects exerted on the circulation and the myocardium

Antagonism of neurohormonal systems forms the basis of modern therapy for HFrEF

Is that it ?

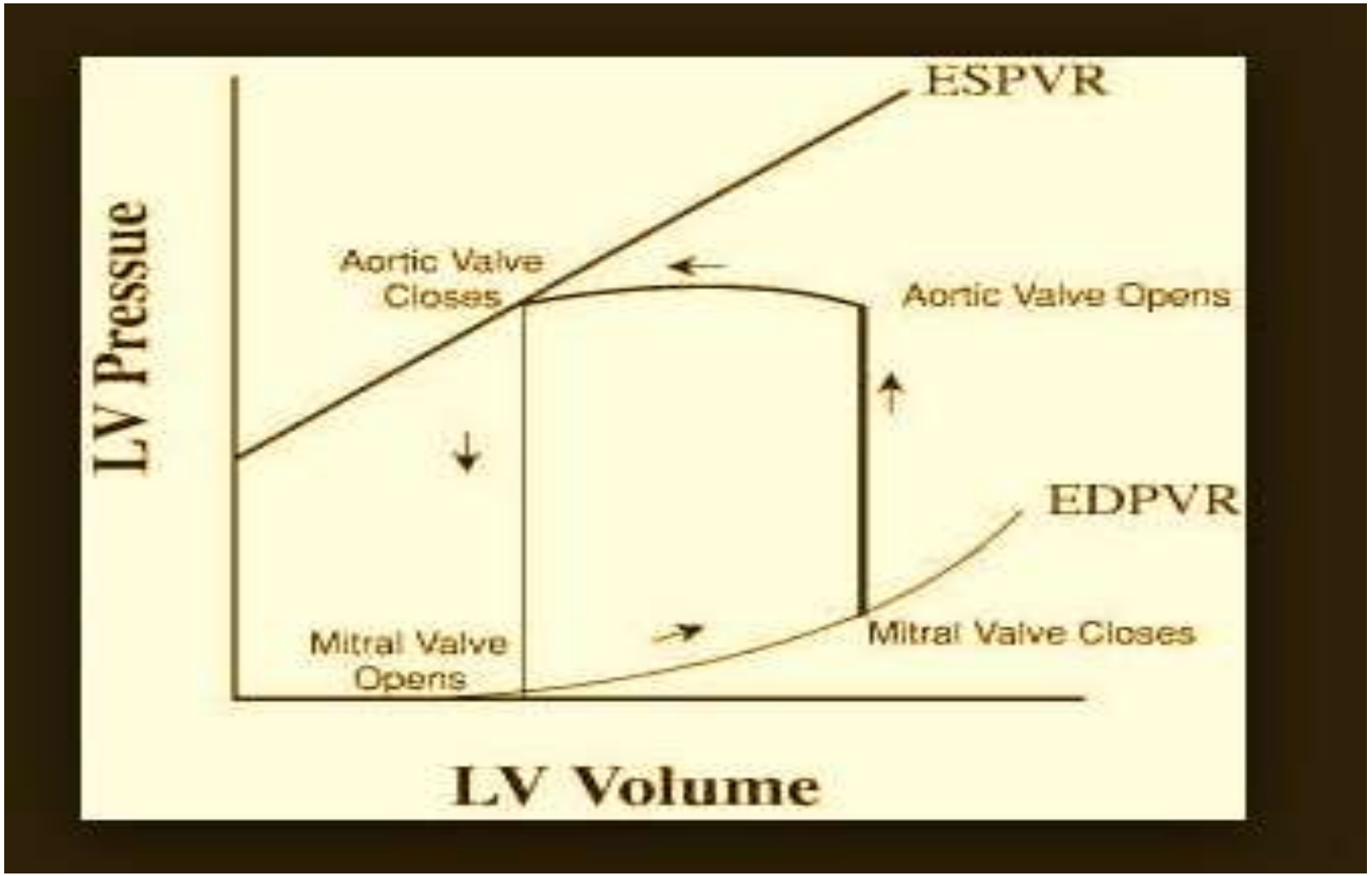
- Lot of patients with so called “stable” chronic ds are indeed not stable with most patients exhibiting elevated cardiac biomarkers such as troponin reflective of continued cardiomyocyte necrosis or loss. This is reflective of a underlying dynamic process contributing to ds progression

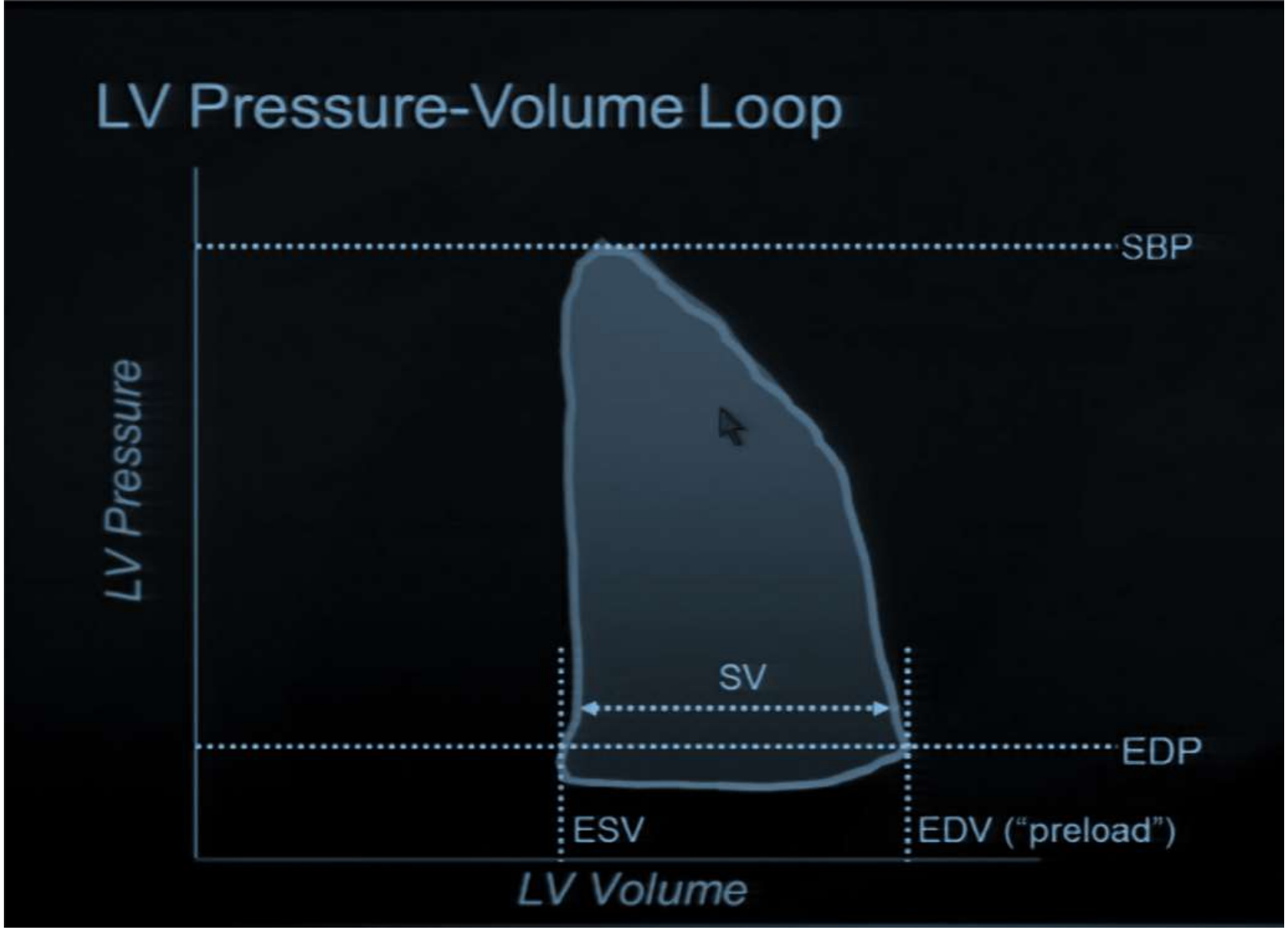
Mechanisms that drive LV Dysfunction: *Intrinsic*

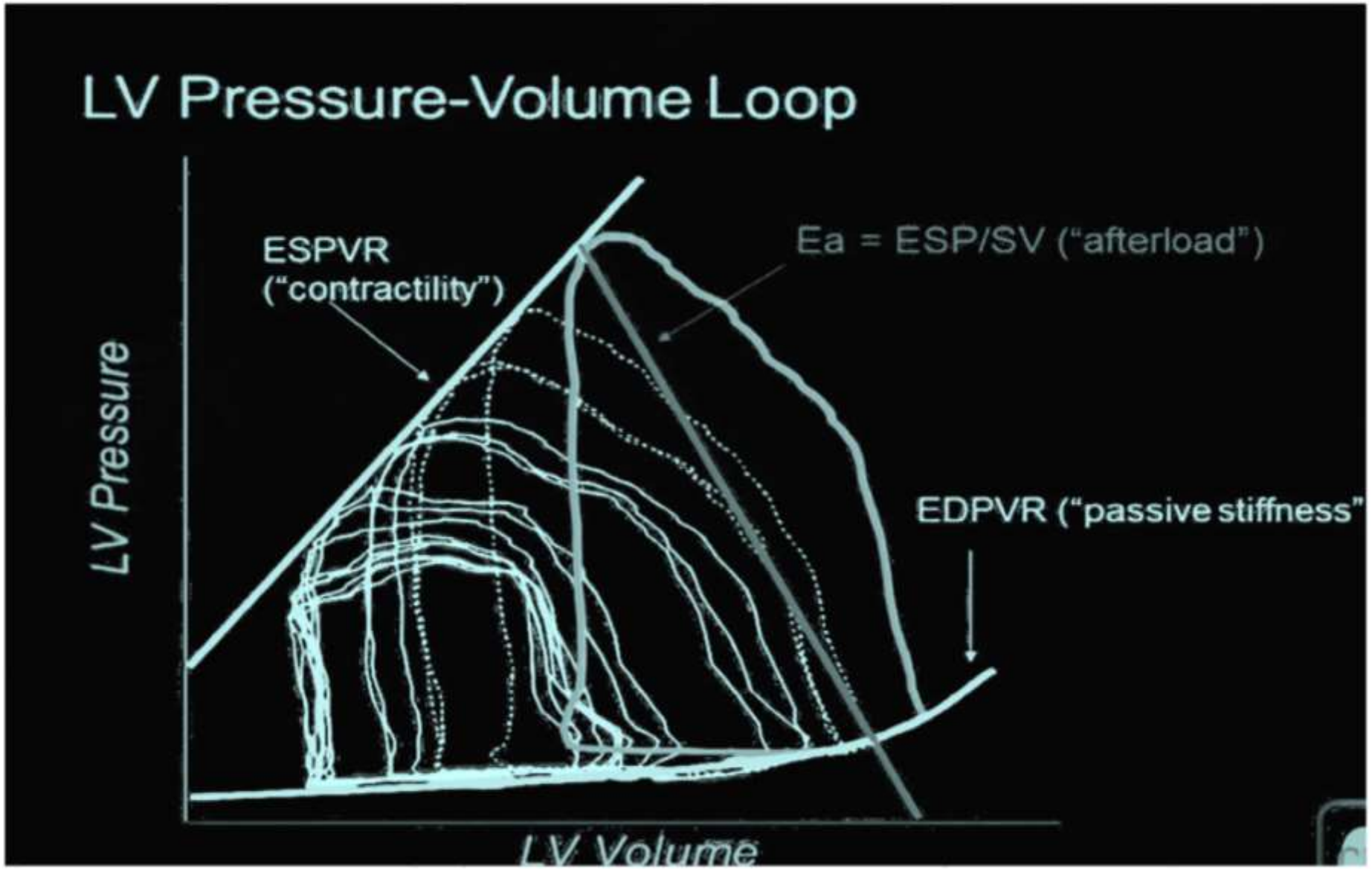
1. Cardiac Apoptosis – cardiomyocyte loss is the hallmark of HFrEF. Limited capacity for self renewal so gradual loss f functional units through cell death leads to ds progression
2. Mitochondrial abnormalities: abnormalities of ATP synthesis and excess production of ROS.
3. Impaired intracellular calcium cycling (calcium signalling plays an important role in modulating systolic and diastolic function and in regulating excitation-contraction coupling. Abnormalities of intracellular calcium handling such a reduced SERCA activity, impaired phosphorylation of phospholamban and ryanodine channel leading to calcium leaks. This ca cause calcium overload, arrhythmias, cardiomyocyte dysfunction and death
4. Wall stress (Laplace's law, increased MVO2)
5. Fibrosis and cardiomyocyte hypertrophy (reactive interstitial fibrosis, reduced capillary density, increased oxygen diffusion all causing hypoxia and increasing LV stiffness and contributing to LV dysfunction

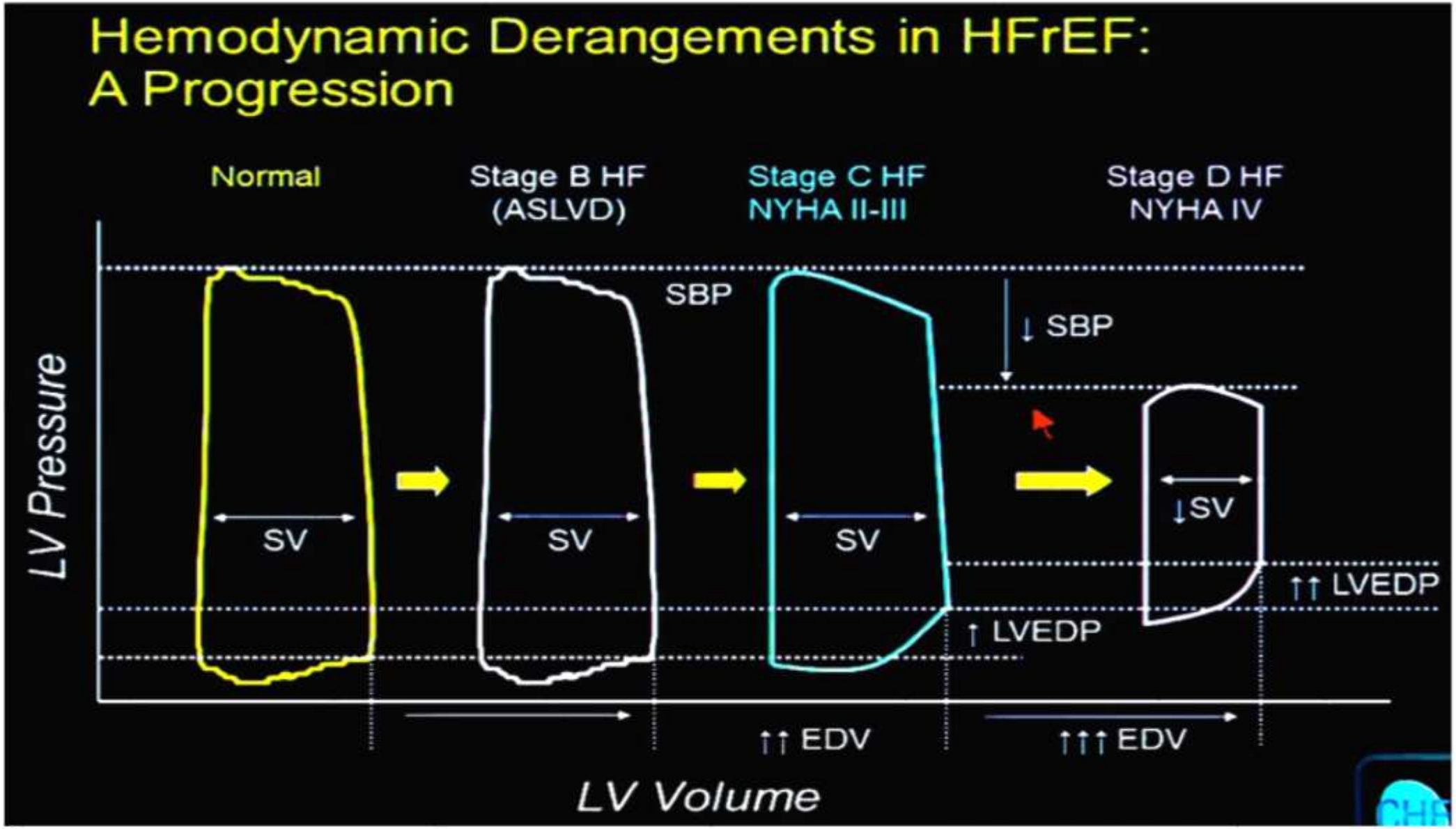
Physiology

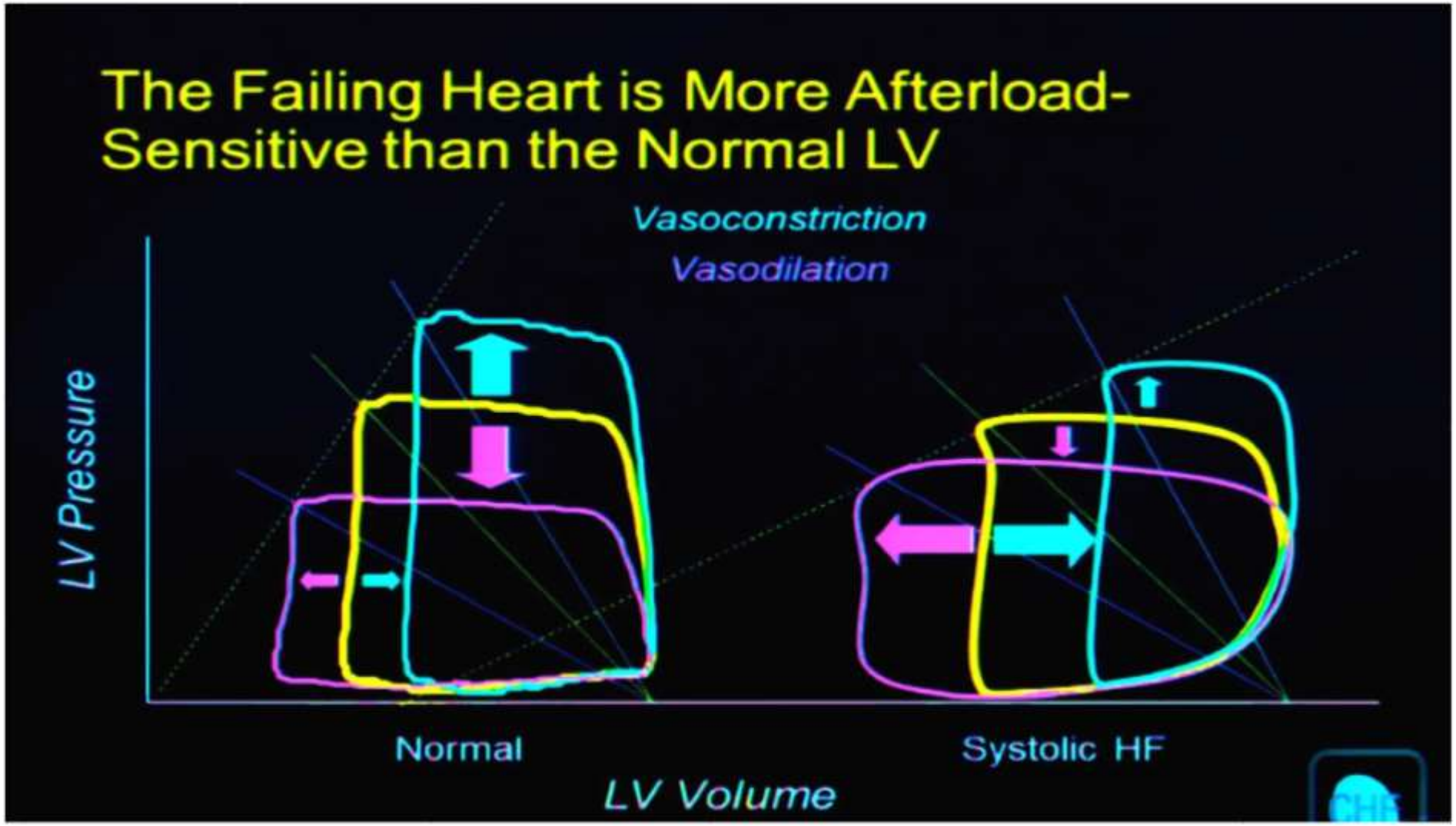
- Hemodynamics and PV loops

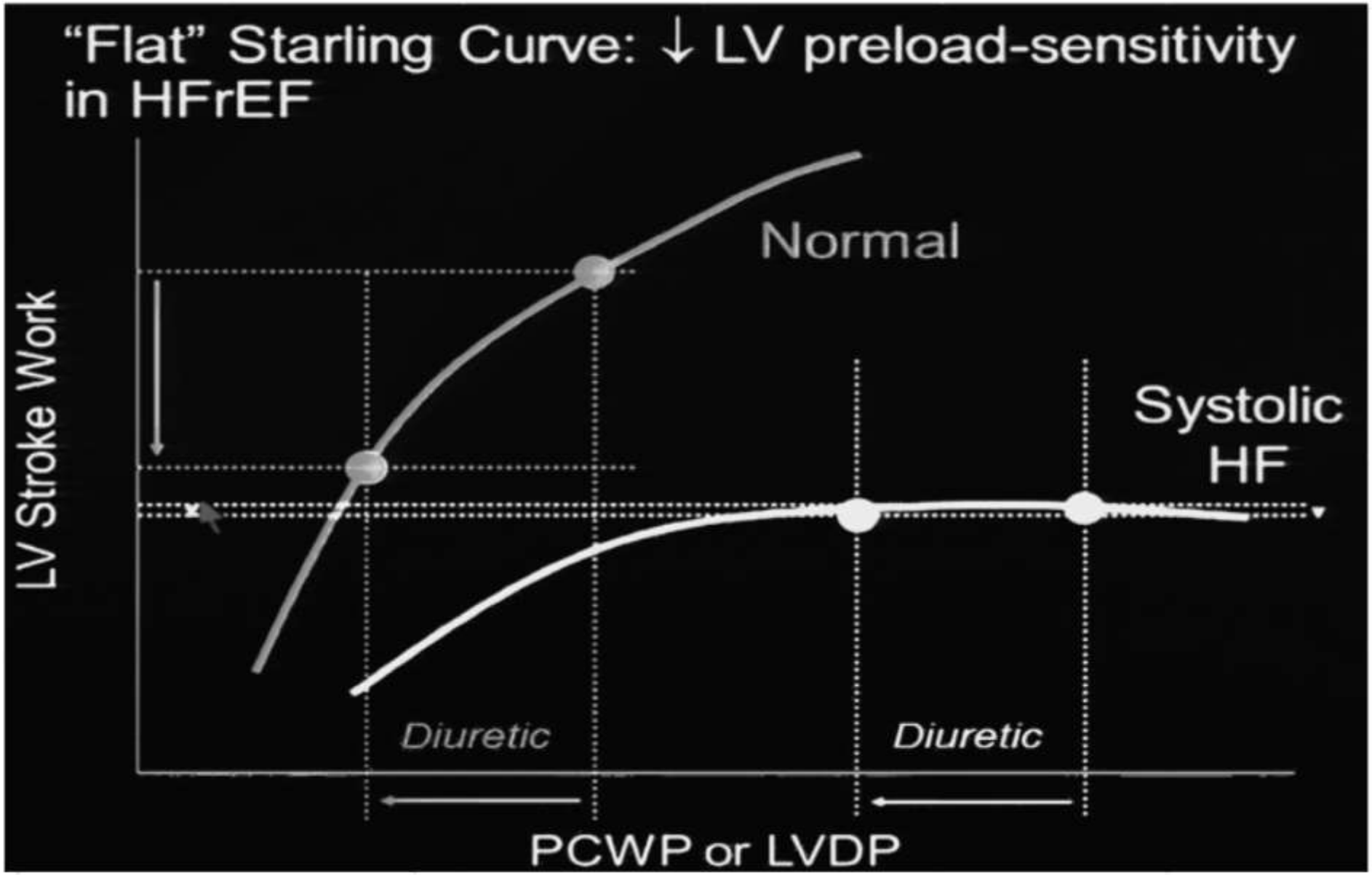

ESPVR
LV Pressue
Aortic Valve Closes
Aortic Valve Opens
EDPVR
Mitral Valve Opens
Mitral Valve Closes
LV Volume

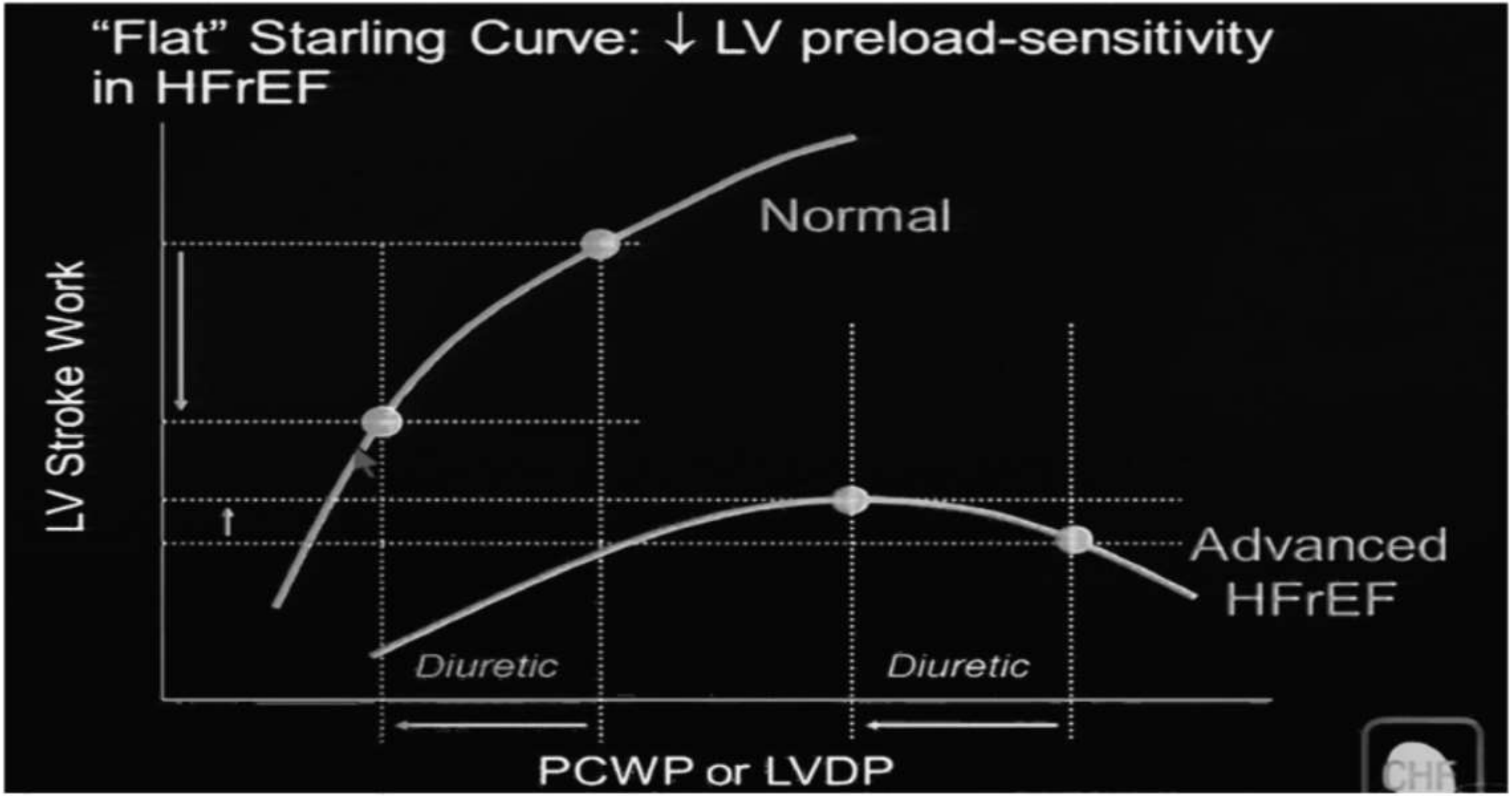

LV Pressure-Volume Loop
SBP
LV Pressure
SV
EDP
ESV
EDV ("preload")
LV Volume

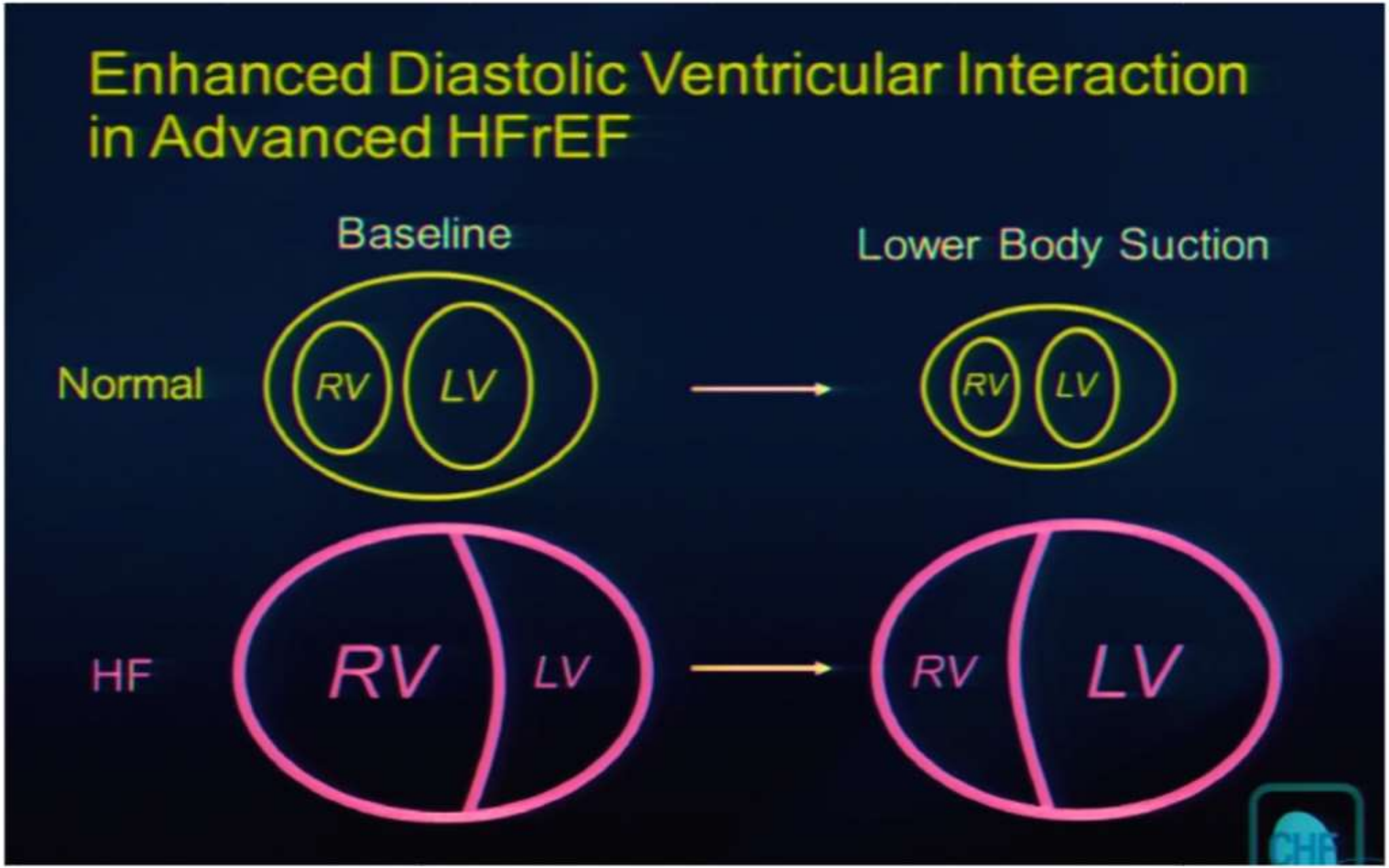

LV Pressure-Volume Loop
ESPVR
("contractility")
Ea = ESP/SV ("afterload")
EDPVR ("passive stiffness"
LV Pressure
LV Volume

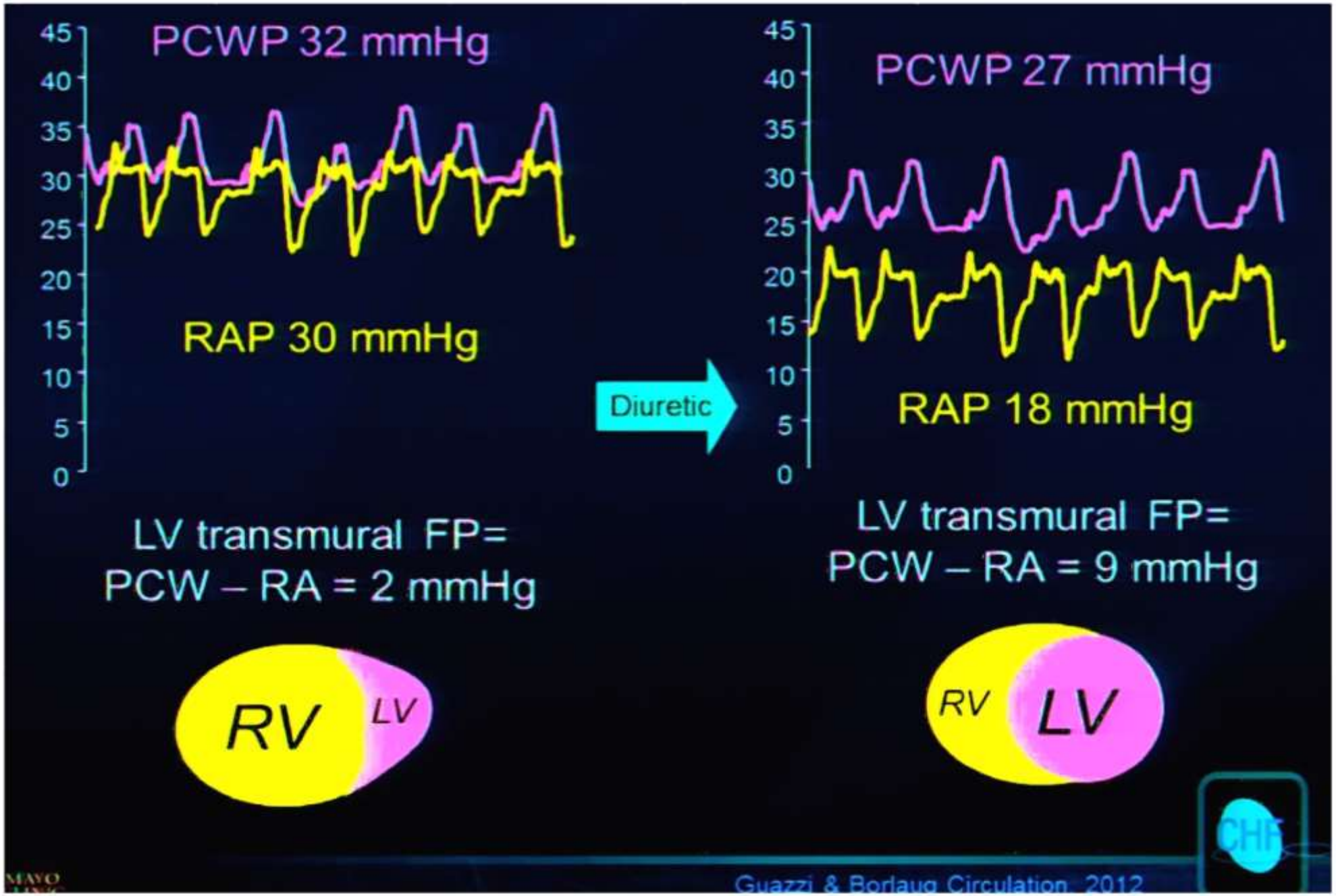

Hemodynamic Derangements in HFrEF:
A Progression
Normal
Stage B HF
(ASLVD)
Stage C HF
NYHA II-III
Stage D HF
NYHA IV
SBP
↓ SBP
SV
SV
SV
↓SV
↑↑ LVEDP
↑ LVEDP
↑↑ EDV
↑↑↑ EDV
LV Pressure
LV Volume


The Failing Heart is More Afterload-Sensitive than the Normal LV
Vasoconstriction
Vasodilation
LV Pressure
Normal
Systolic HF
LV Volume


"Flat" Starling Curve: ↓ LV preload-sensitivity in HFrEF
Normal
Systolic HF
LV Stroke Work
Diuretic
Diuretic
PCWP or LVDP

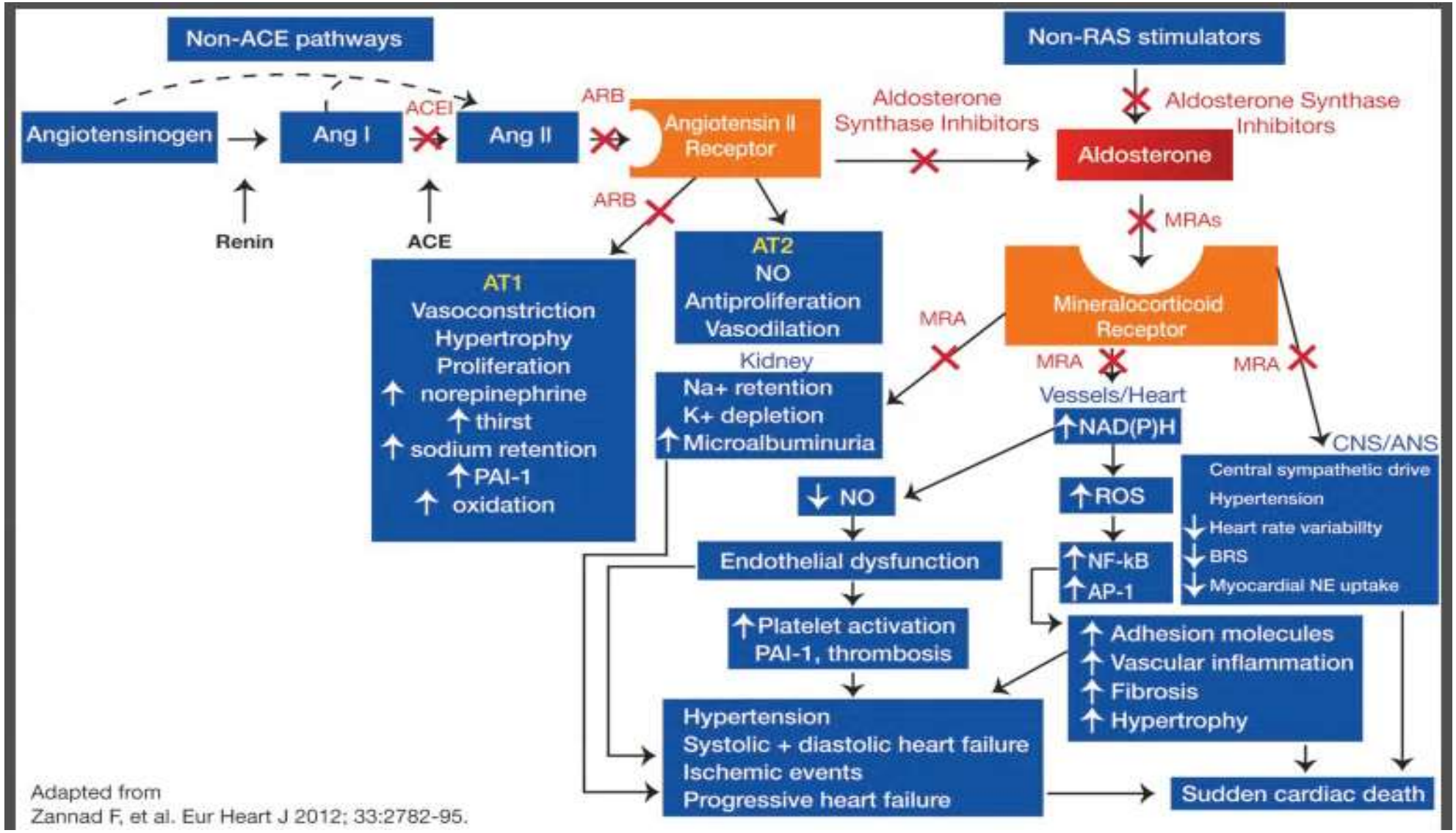

"Flat" Starling Curve: ↓ LV preload-sensitivity in HFrEF
LV Stroke Work
Normal
Advanced HFrEF
Diuretic
Diuretic
PCWP or LVDP


Enhanced Diastolic Ventricular Interaction in Advanced HFrEF
Baseline
Lower Body Suction
Normal
RV
LV
RV
LV
HF
RV
LV
RV
LV

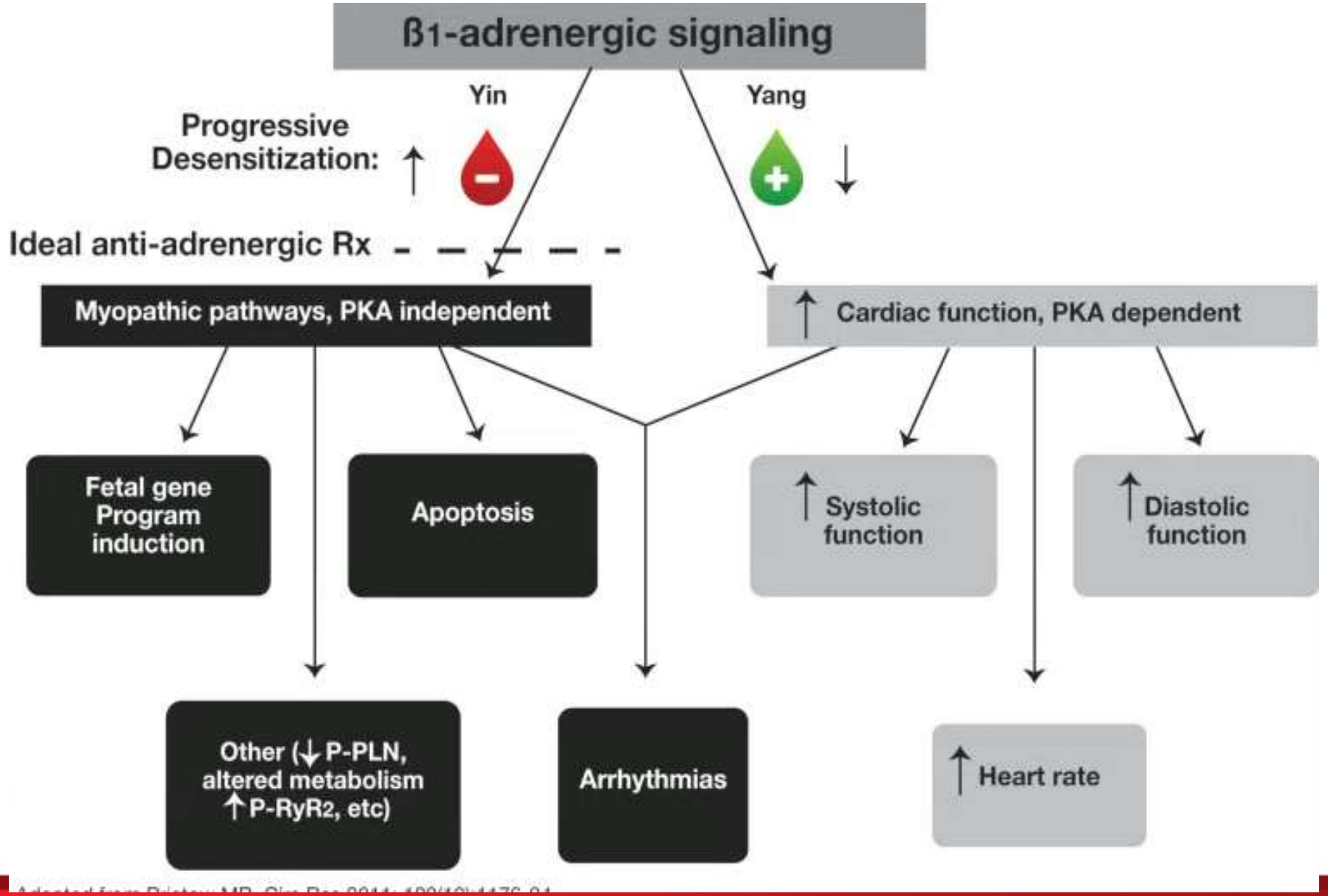

PCWP 32 mmHg
RAP 30 mmHg
LV transmural FP=
PCW – RA = 2 mmHg
RV
LV
Diuretic
PCWP 27 mmHg
RAP 18 mmHg
LV transmural FP=
PCW – RA = 9 mmHg
RV
LV
Guazzi & Borlaug Circulation 2012

Therapeutics

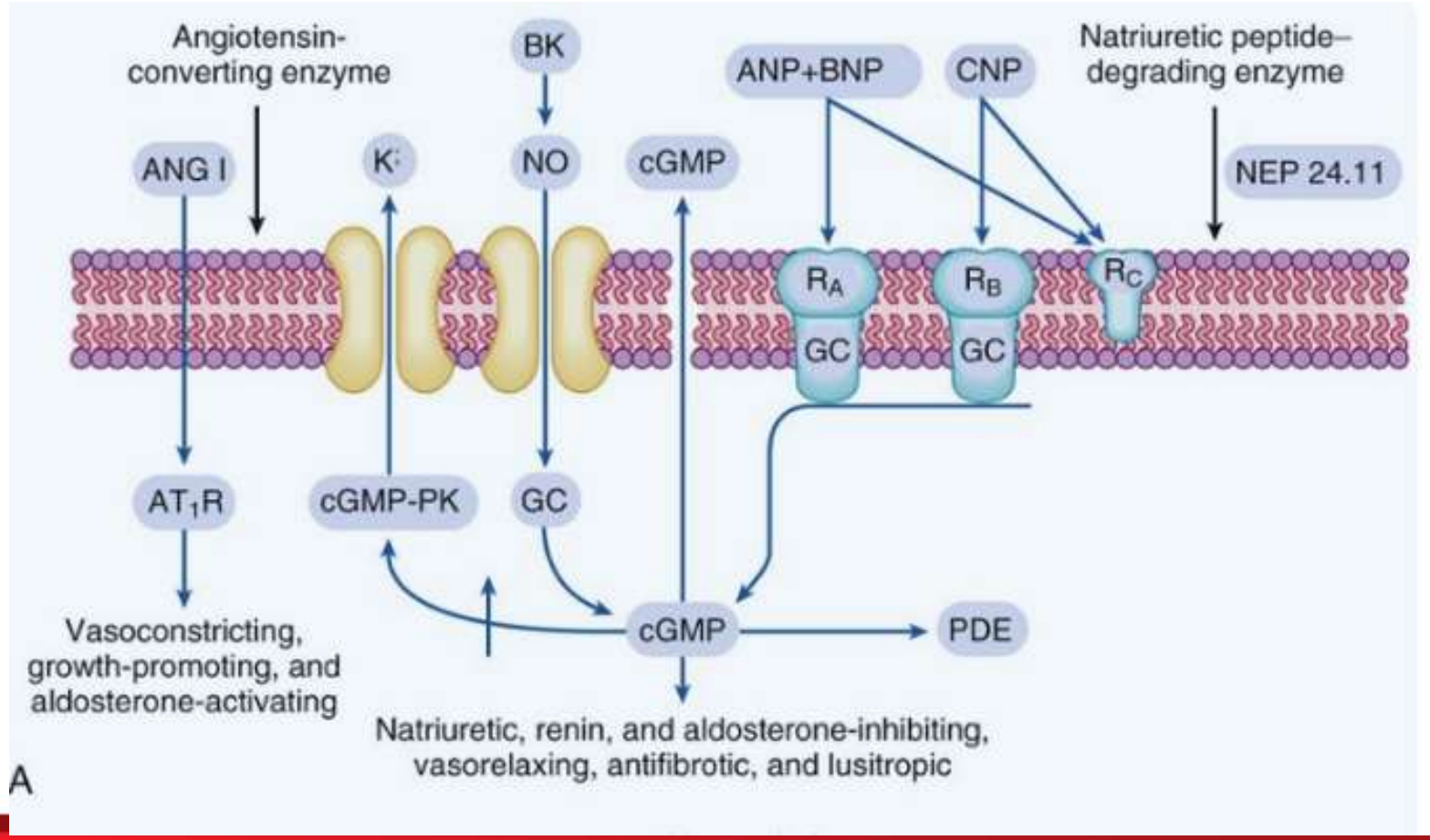
- Targeting the Neuroharmonal pathways
- Treating at the “periphery”
- Despite blockade of the “maladaptive” processes there is still progression of disease



Adapted from
Zannad F, et al. Eur Heart J 2012; 33:2782-95.


ß1-adrenergic signaling
Yin
Yang
Progressive Desensitization:
Ideal anti-adrenergic Rx
Myopathic pathways, PKA independent
Cardiac function, PKA dependent
Fetal gene Program induction
Apoptosis
Systolic function
Diastolic function
Other (↓ P-PLN, altered metabolism ↑ P-RyR2, etc)
Arrhythmias
Heart rate

Mechanism of ARNI



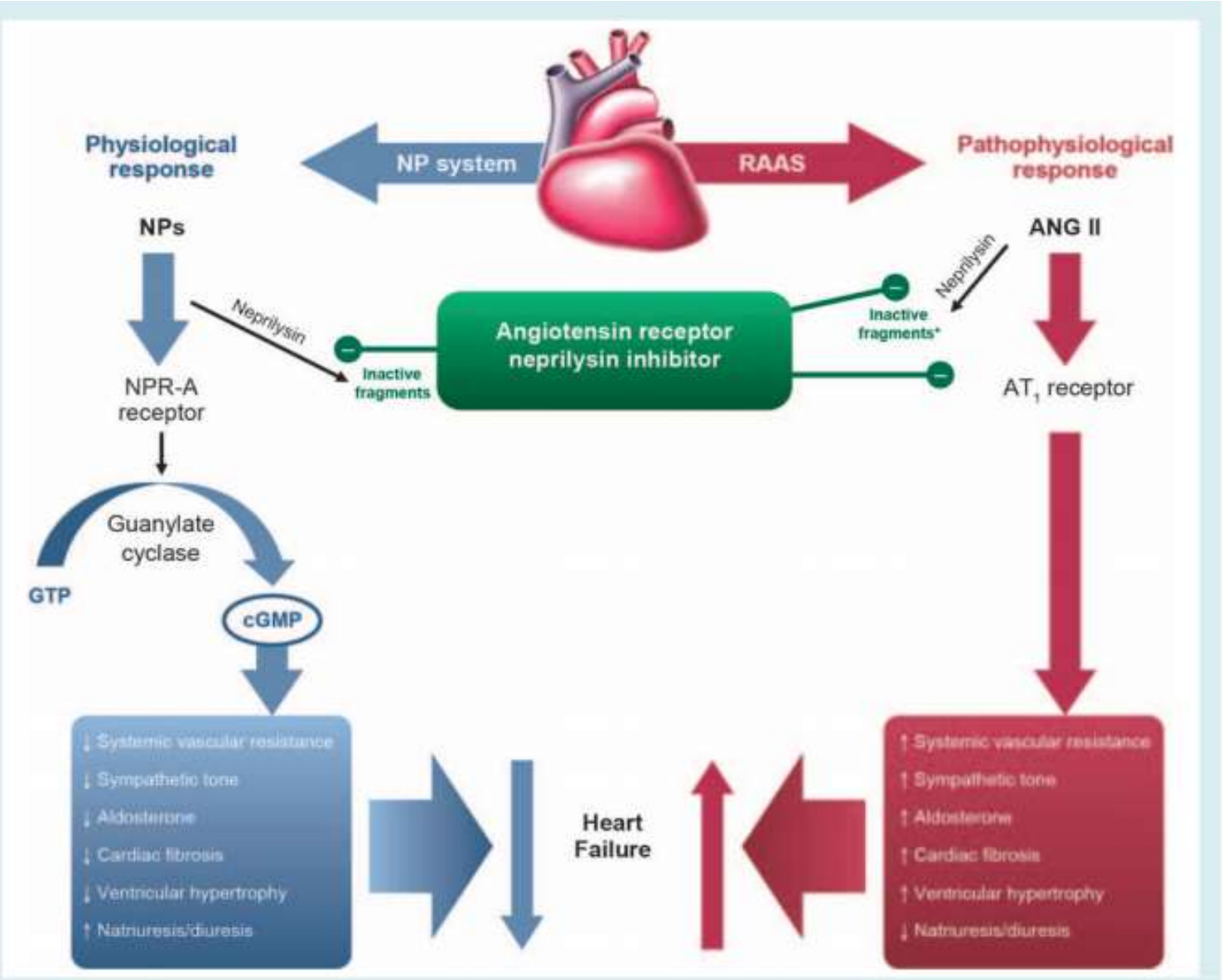
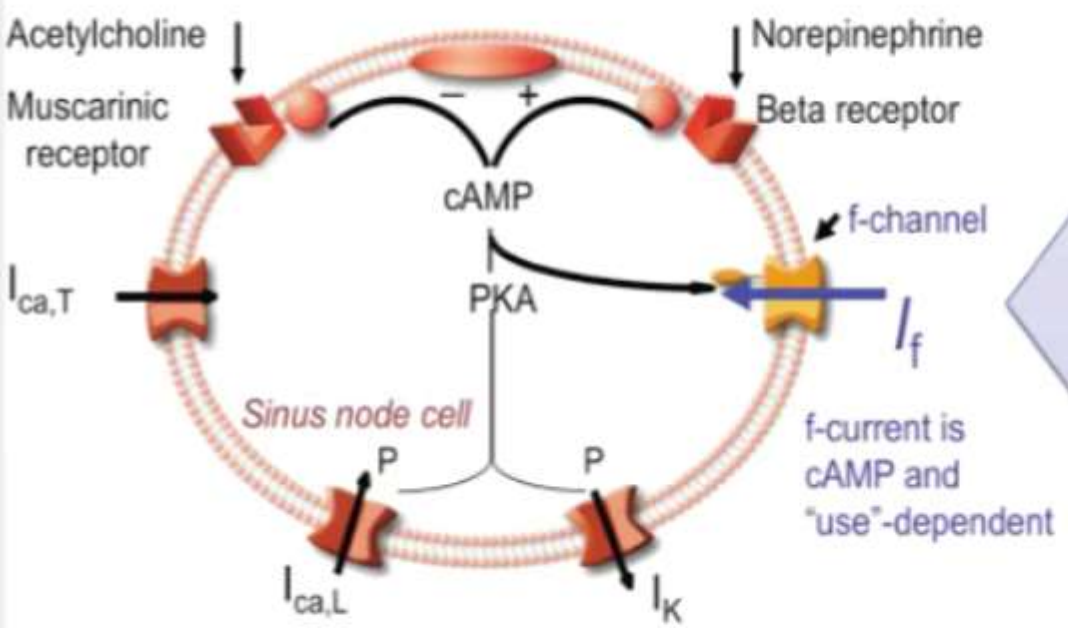


Figure 1 Mechanism of action for sacubitril/valsartan.[93] Reprinted from Langenickel TH, Dole WP. Angiotensin receptor–neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. *Drug Discov Today Ther Strateg* 2013; **9**:e131–e139. ANG, angiotensin; AT_1, angiotensin-II type 1; cGMP, cyclic guanosine monophosphate; GTP, guanosine-5'-triphosphate; NP, natriuretic peptide (e.g. atrial natriuretic peptide, BNP); NPR-A, NP receptor-A; RAAS, renin–angiotensin–aldosterone system. **In vitro* evidence.

Heart rate control

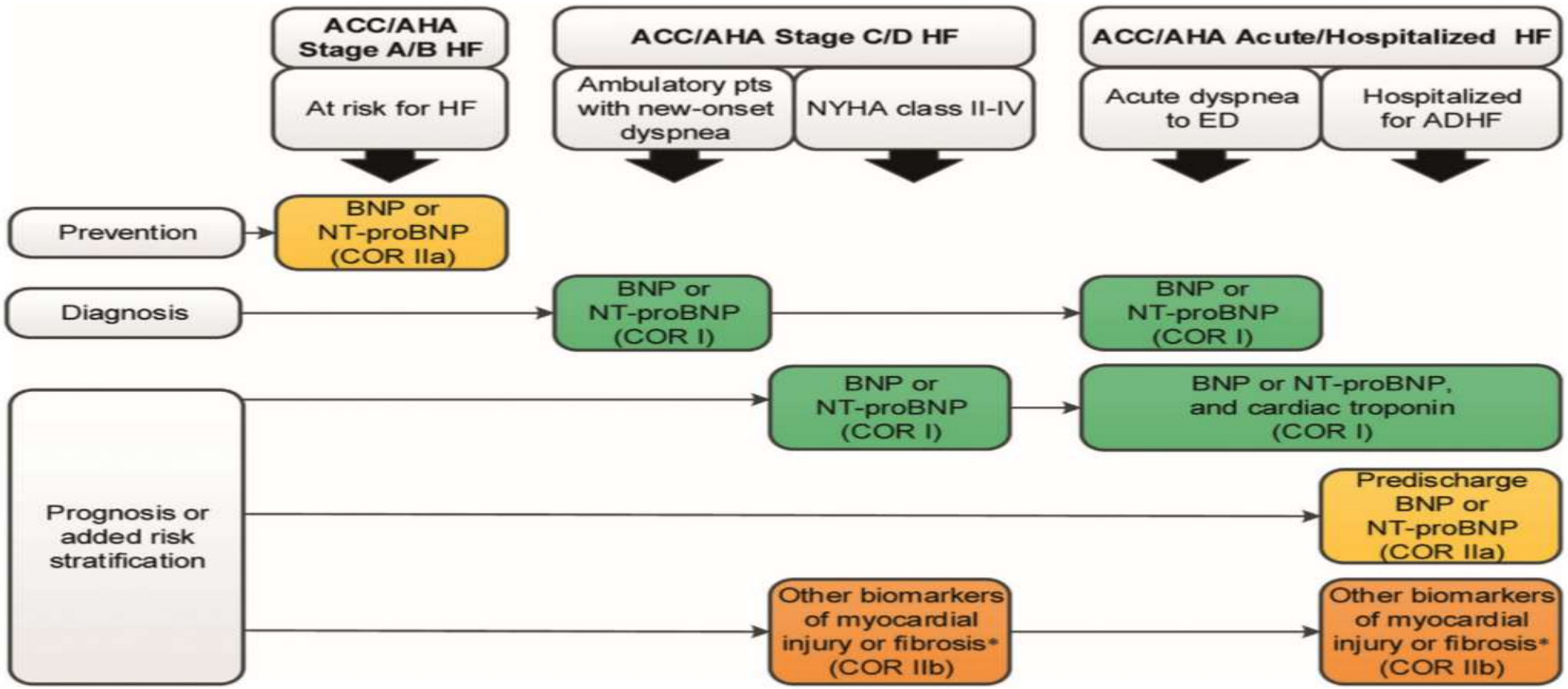


f-current is cAMP and "use"-dependent

Ivabridine: Postulated Mechanisms of Benefit for HR Reduction

- Decreased myocyte ischemia
- Increased energy for myocyte maintenance and repair
- Decreased LVEDP, cardiac volumes and remodelling
- Increased LV relaxation
- Increased endothelial cell proliferation and eNOS
- Increased collateral function

FIGURE 1 **Biomarkers Indications for Use**



Colors correspond to COR in Table 1.

*Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and high-sensitivity troponin.

ACC indicates American College of Cardiology; AHA, American Heart Association; ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; COR, Class of Recommendation; ED, emergency department; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and pts, patients.

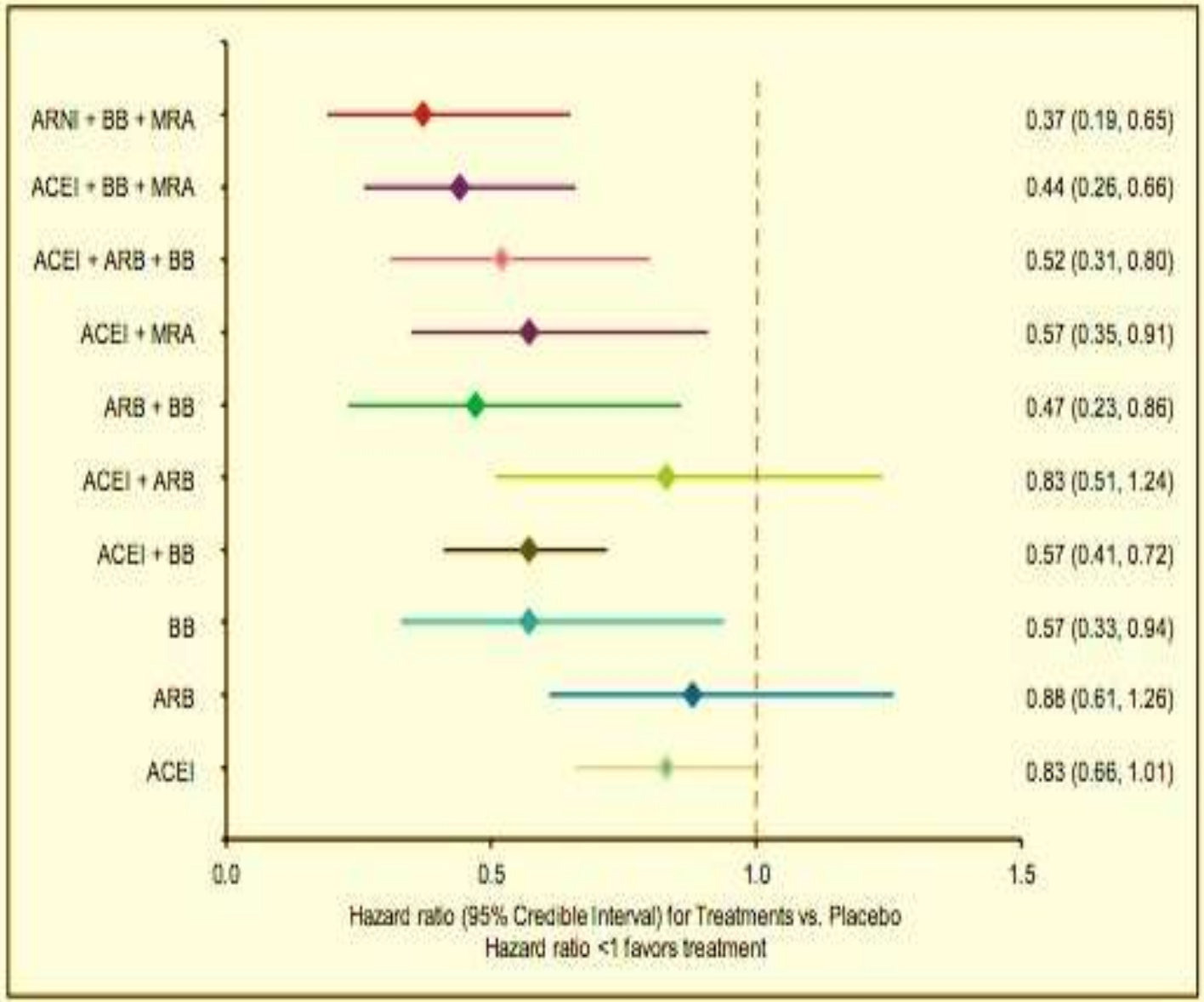


Figure 5. Results of random effect network meta-analysis for all-cause mortality: hazard ratios for intervention versus placebo for all-cause mortality and 95% credible intervals. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; and MRA, mineralocorticoid receptor antagonist.

Progression to Stage D or Advanced HF

Advanced HF is the presence of progressive and/or persistent severe symptoms of heart failure despite optimized medical, surgical and device therapy

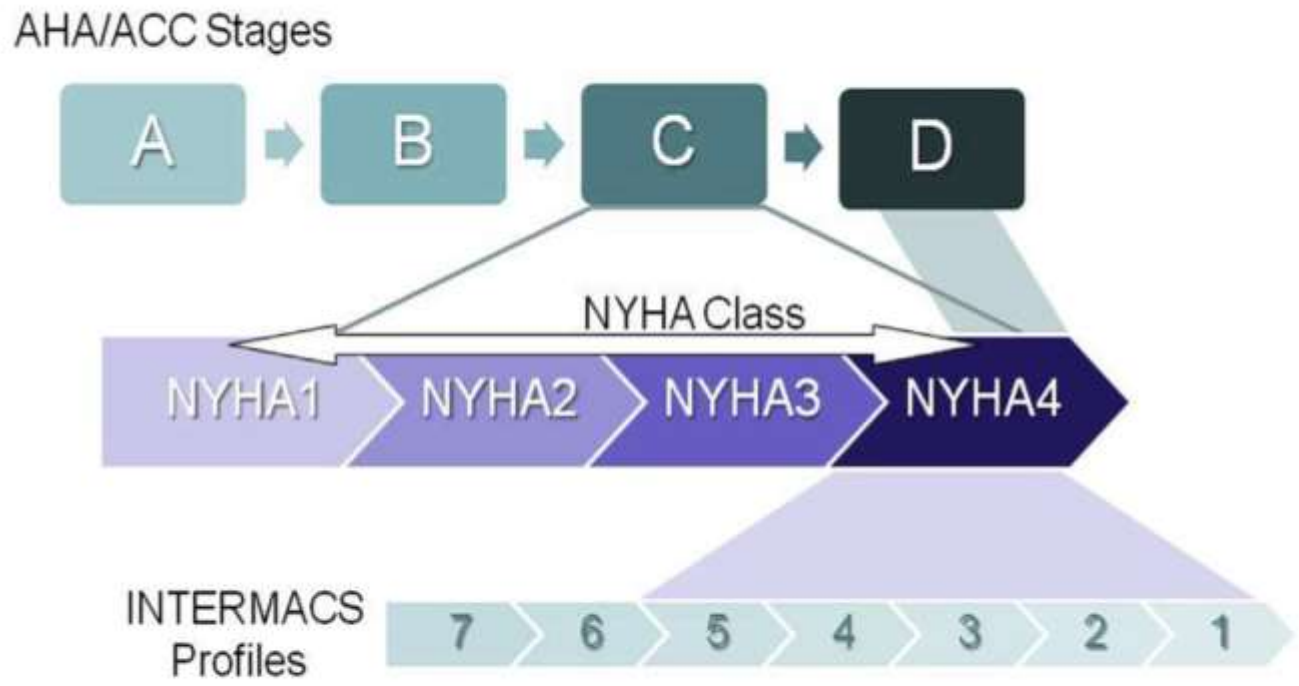
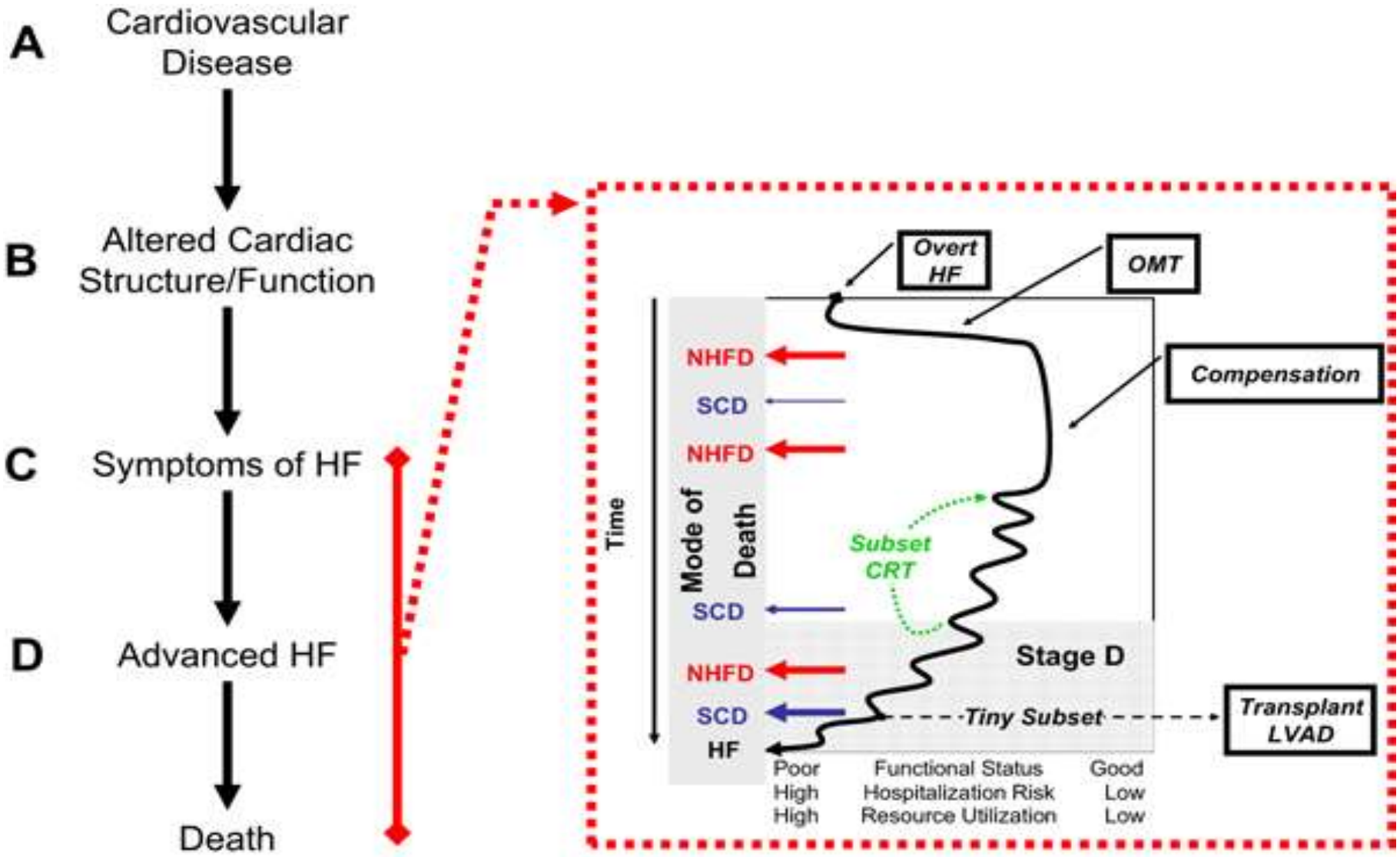


Fig. 1. Classification schemes for heart failure severity. Overlapping classification systems provide complementary descriptive and prognostic information for patients with advanced heart disease. NYHA classifies dynamic functional limitation, the American Heart Association/American College of Cardiology-Stages of Heart Failure highlight antecedent risk factors and disease progression, while the INTERMACS patient profiles integrate symptom burden and ongoing measures use to treat evolving shock.

HFrEF now becomes a systemic ds

- Passive liver congestion, ascites
- Bone marrow dysfunction and anemia
- Endothelial dysfunction
- Sleep disordered breathing
- Renal dysfunction
- Skeletal muscle abnormalities
- Persistent venous congestion causes inflammation with elevated biomarkers and systemic inflammation



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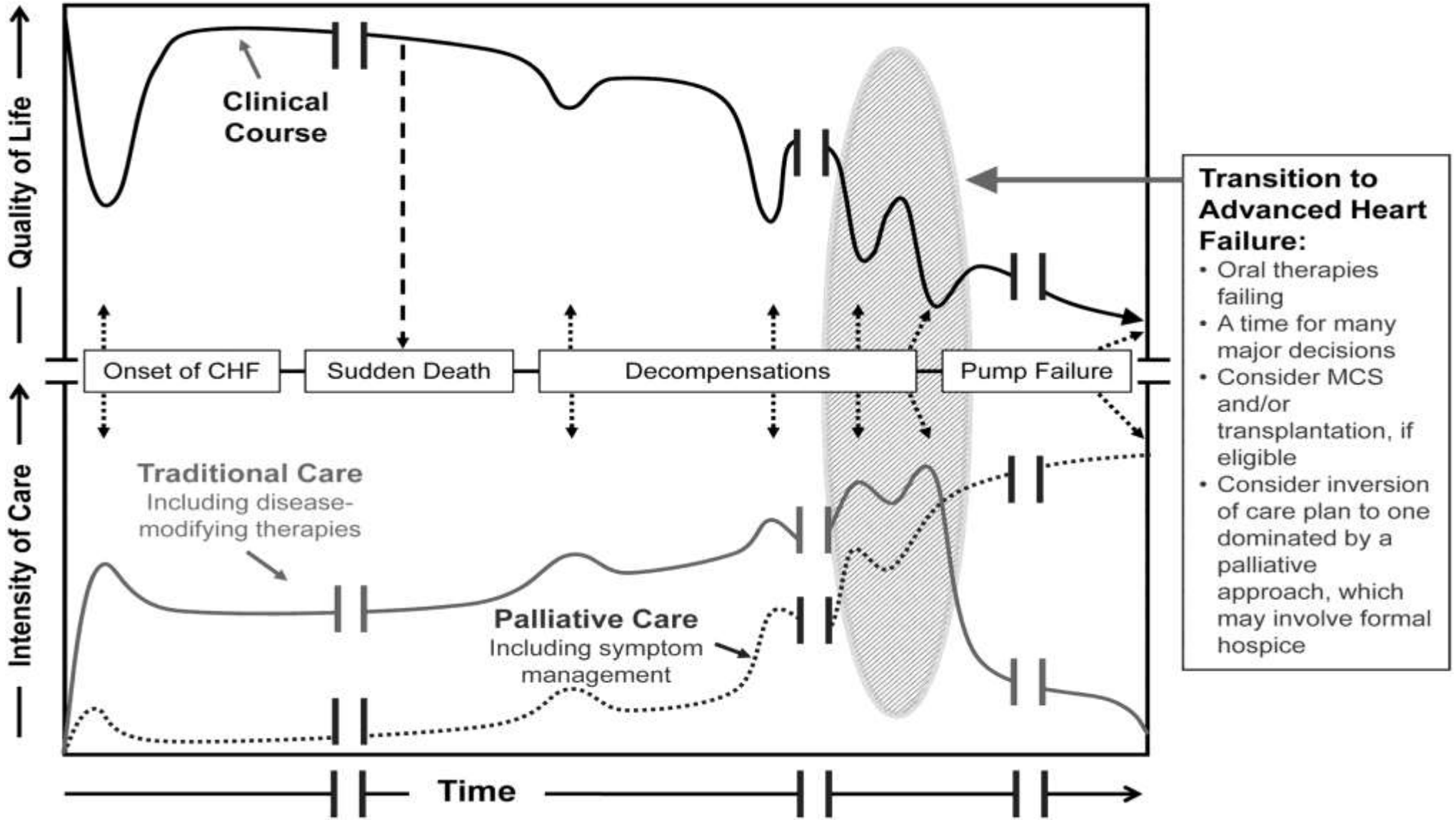
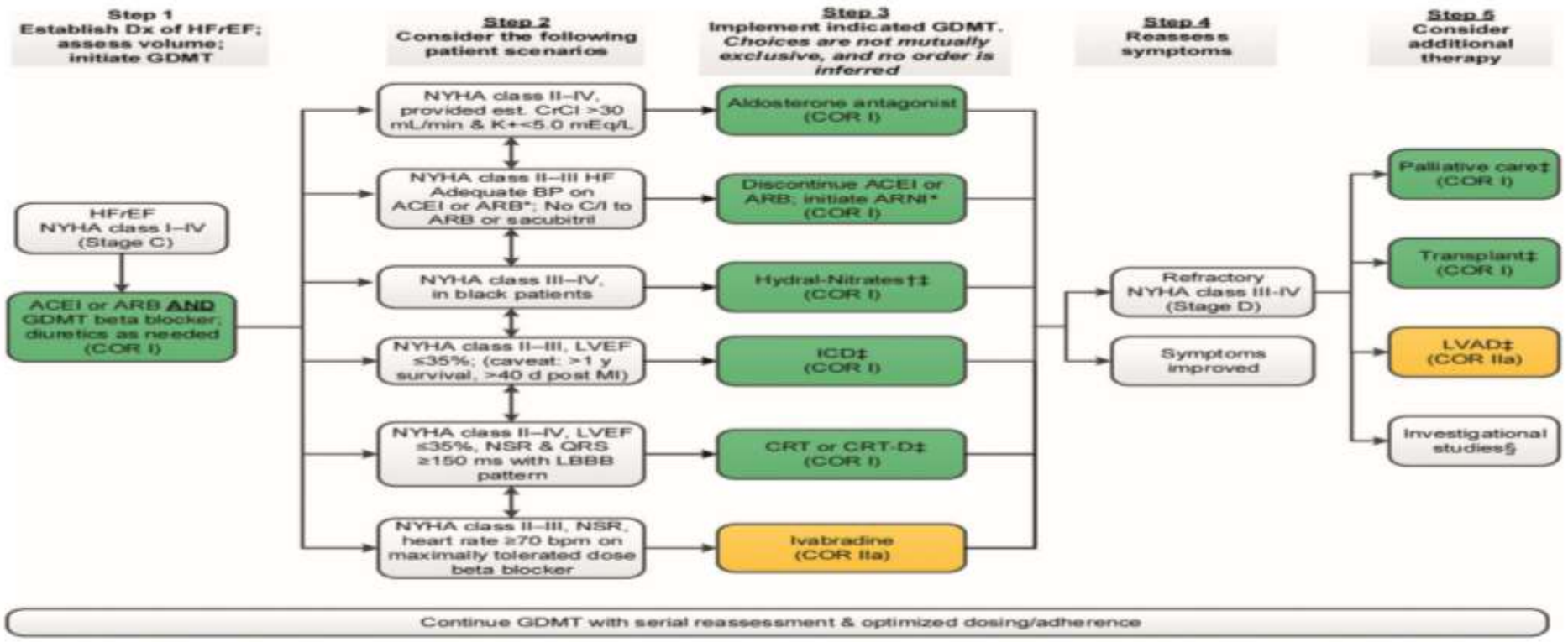
Volume 17, Issue 4, pages 160-168, 21 JUL 2011 DOI: 10.1111/j.1751-7133.2011.00246.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1751-7133.2011.00246.x/full#f1



Larry A. Allen et al. Circulation. 2012;125:1928-1952

ACC/AHA/HFSA focused updated

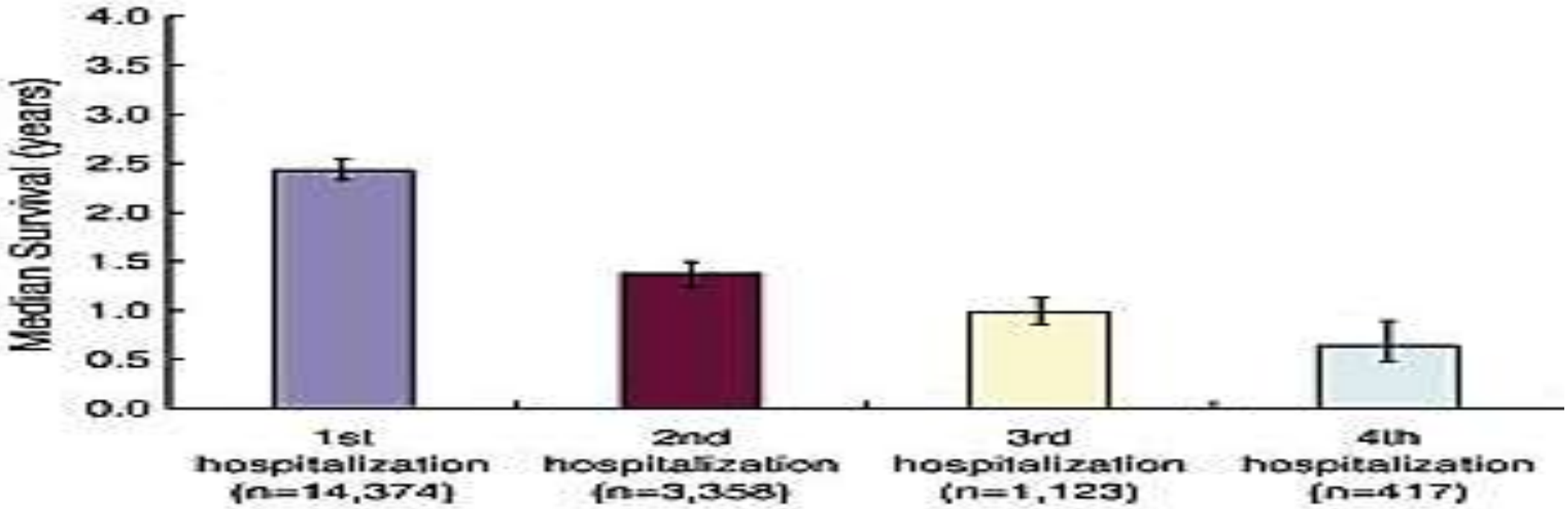
FIGURE 2 Treatment of HF*r*EF Stage C and D



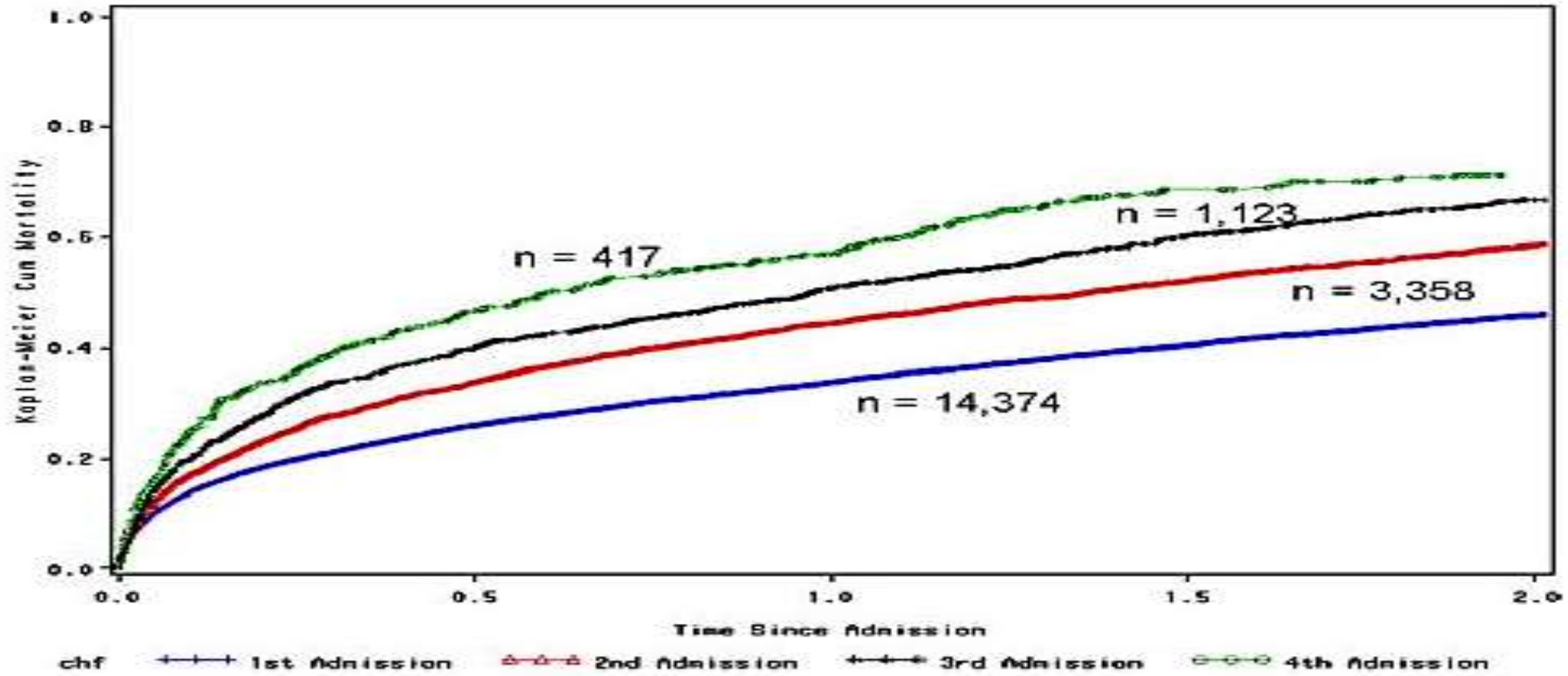
Colors correspond to COR in Table 1. For all medical therapies, dosing should be optimized and serial assessment exercised.
*See text for important treatment directions.
†Hydral-Nitrates green box: The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully monitored. ‡See 2013 HF guideline (9).
§Participation in investigational studies is also appropriate for stage C, NYHA class II and III HF.
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor-blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; COR, Class of Recommendation; CrCl, creatinine clearance; CRT-D, cardiac resynchronization therapy-device; Dx, diagnosis; GDMT, guideline-directed management and therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate hydral-nitrates; K+, potassium; LBBB, left bundle-branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSR, normal sinus rhythm; and NYHA, New York Heart Association.

Impact of recurrent heart failure hospitalization on mortality. Median survival (50% mortality) with 95% confidence limits in patients with heart failure after each heart failure hospitalization. (From Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J 2007;154(2):260-)

Figure 2

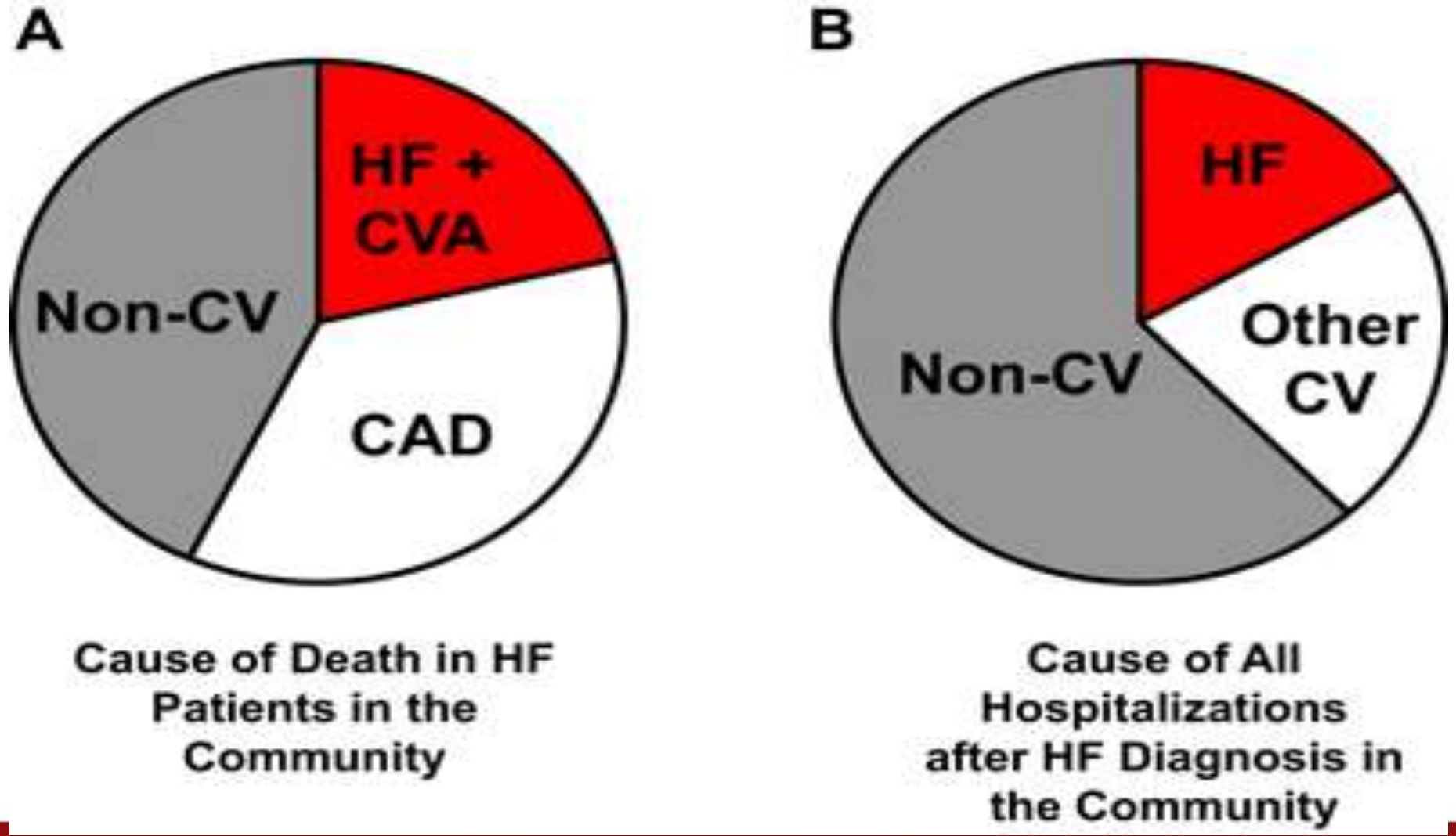


Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.



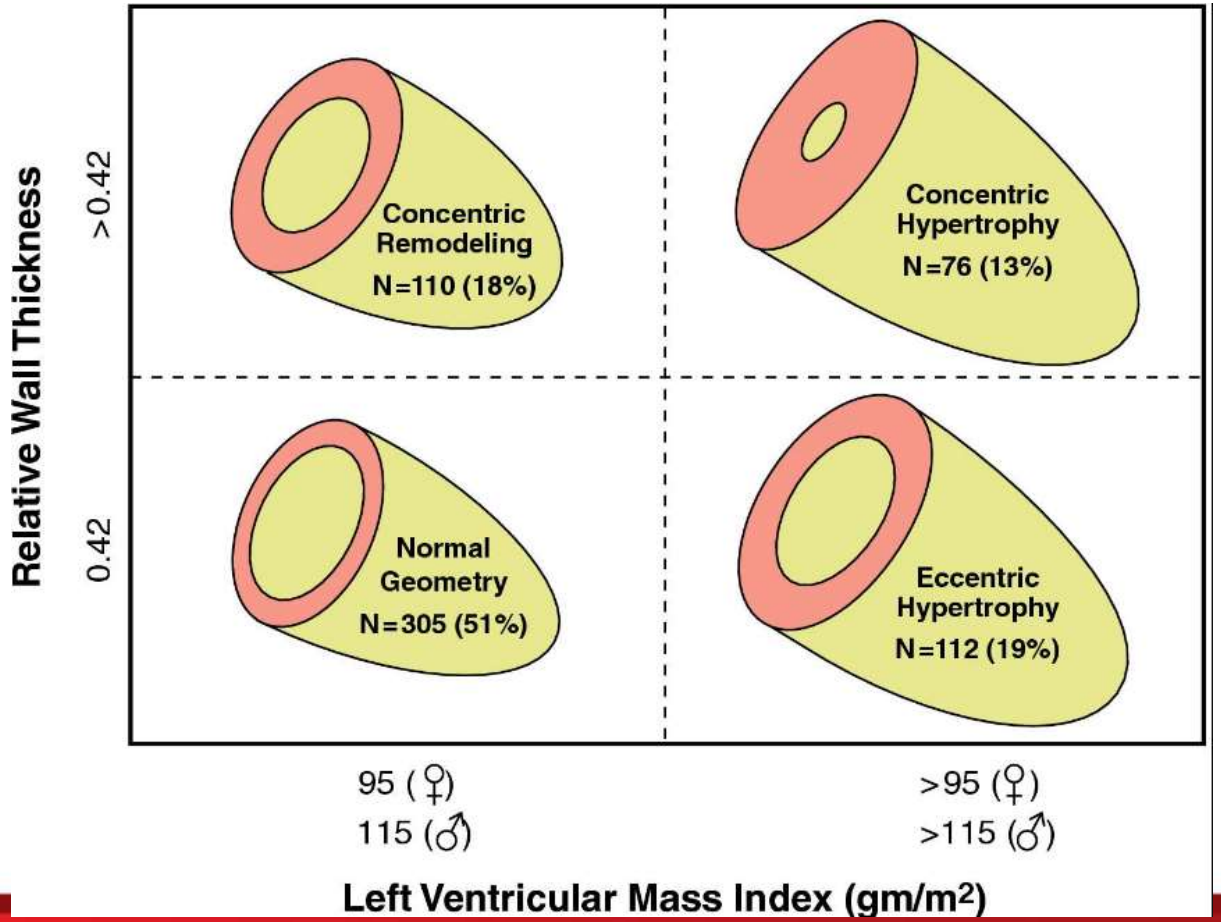
Kaplan-Meier cumulative mortality curve for all-cause mortality after each subsequent hospitalization for HF.

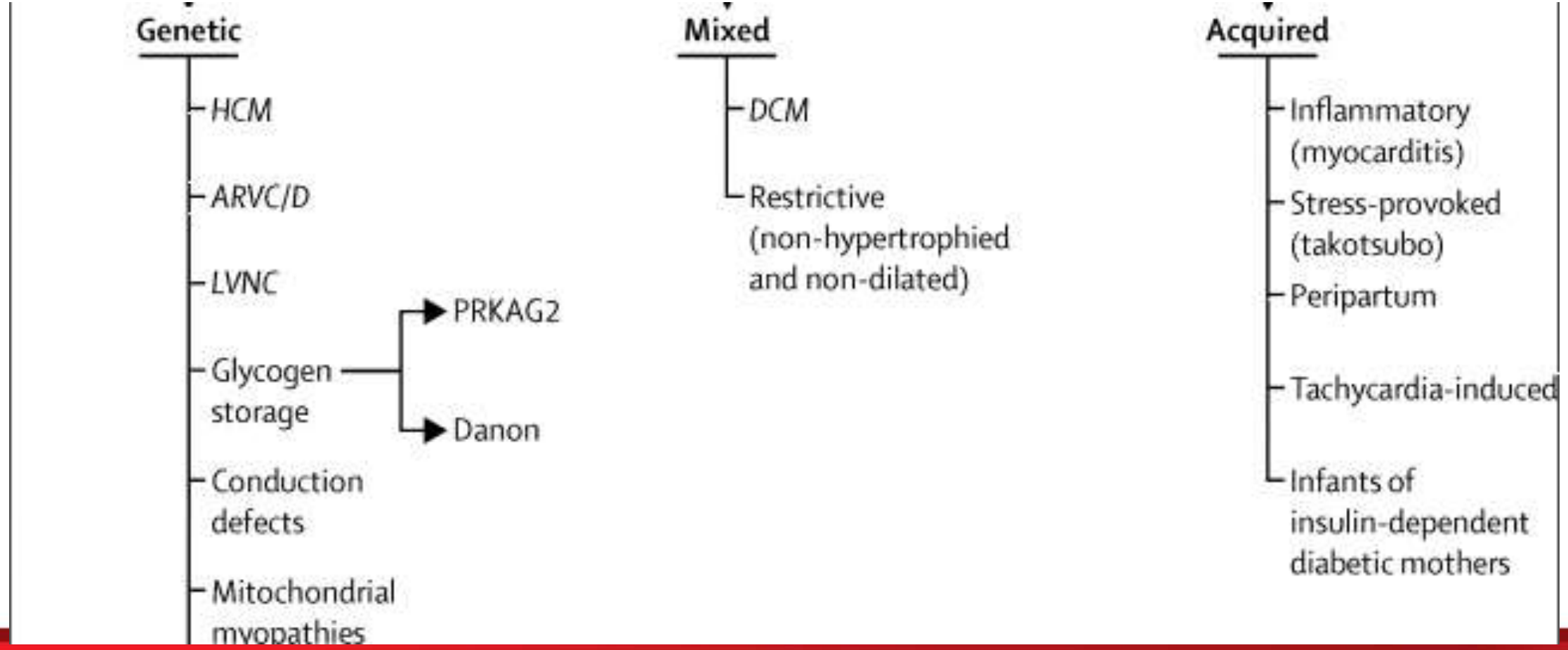
Who Has Advanced Heart Failure? Definition and Epidemiology



Congestive Heart Failure
Volume 17, Issue 4, pages 160-168, 21 JUL 2011 DOI: 10.1111/j.1751-7133.2011.00246.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1751-7133.2011.00246.x/full#f3

- END OF PRESENTATION


Relative Wall Thickness
>0.42
0.42
Concentric Remodeling
N=110 (18%)
Concentric Hypertrophy
N=76 (13%)
Normal Geometry
N=305 (51%)
Eccentric Hypertrophy
N=112 (19%)
95 (♀)
115 (♂)
>95 (♀)
>115 (♂)
Left Ventricular Mass Index (gm/m2)


Genetic
HCM
ARVC/D
LVNC
Glycogen storage
PRKAG2
Danon
Conduction defects
Mitochondrial myopathies
Mixed
DCM
Restrictive (non-hypertrophied and non-dilated)
Acquired
Inflammatory (myocarditis)
Stress-provoked (takotsubo)
Peripartum
Tachycardia-induced
Infants of insulin-dependent diabetic mothers

Titin (*TTN*)	20–25% of familial DCM; autosomal dominant mode
Lamin A/C (*LMNA*)	~5% of familial DCM; autosomal dominant mode
Myosin heavy chain 7 (*MYH7*)	~4% of familial DCM; autosomal dominant mode
Troponin T (*TNNT2*)	~2% of familial DCM; autosomal dominant mode
Myosin-binding protein C (*MYBPC3*)	~2% of familial DCM; autosomal dominant mode
Myopalladin (*MYPN*)	~2% of familial DCM; autosomal dominant mode
Sodium channel α unit (*SCN5A*)	~2% of familial DCM; autosomal dominant mode
Phospholamban (*PLN*)	~1% of familial DCM; autosomal dominant mode
Neuromuscular disorders	
Duchenne muscular dystrophy (*DMD*)	X-linked mode; creatine kinase elevation
Becker muscular dystrophy (*BMD*)	X-linked mode; creatine kinase elevation

Infection (myocarditis)	
Viral (including parvovirus B19, HPV6, HIV)	..
Bacterial (including Lyme disease)	Atrioventricular block in Lyme disease
Fungal	..
Parasitic	..
Rickettsial	..
Protozoal	..
Autoimmune diseases	
Organ specific	
Giant cell myocarditis	Multinucleated giant cells; frequent AV block and ventricular arrhythmias
Non-organ specific	
Non-infectious myocarditis	..

Peripartum	
..	Risk factors include multiparity, African descent, familial DCM, autoimmunity
Toxicity and overload	
Ethanol	Risk proportionate to extent and duration of alcohol intake
Cocaine, amphetamines, ecstasy	Chronic users
Other toxins	Arsenic, cobalt, anabolic or androgenic steroids
Iron overload	Transfusions, haemachromatosis
Nutritional deficiency	
Selenium deficiency	Rare, high frequency in some parts of China (Keshan disease)
Thiamine deficiency (Beriberi)	High output heart failure, contributing factors include malnutrition and alcohol abuse
Zinc and copper deficiency	Possible contributors to DCM
Inborn errors of metabolism	
Fatty acid oxidation	Many inborn errors of metabolism cause a mixed phenotype with varying degrees of hypertrophy and reduced systolic function

Antineoplastic drugs	Anthracyclines, antimetabolites, alkylating agents, paclitaxel, hypomethylating agents, monoclonal antibodies, tyrosine kinase inhibitors, immunomodulating agents
Psychiatric drugs	Clozapine, olanzapine, chlorpromazine, risperidone, lithium, methylphenidate, tricyclic antidepressants, phenothiazines
Others	Chloroquine, all-trans retinoic acid, antiretroviral agents
Endocrinology	
Hypothyroidism	..
Hyperthyroidism	..
Cushing's and Addison disease	..
Pheochromocytoma	..
Takotsubo cardiomyopathy	Stress-related
Acromegaly	..
Diabetes mellitus	..

Figure 1. Two-Minute Assessment of Hemodynamic Profile

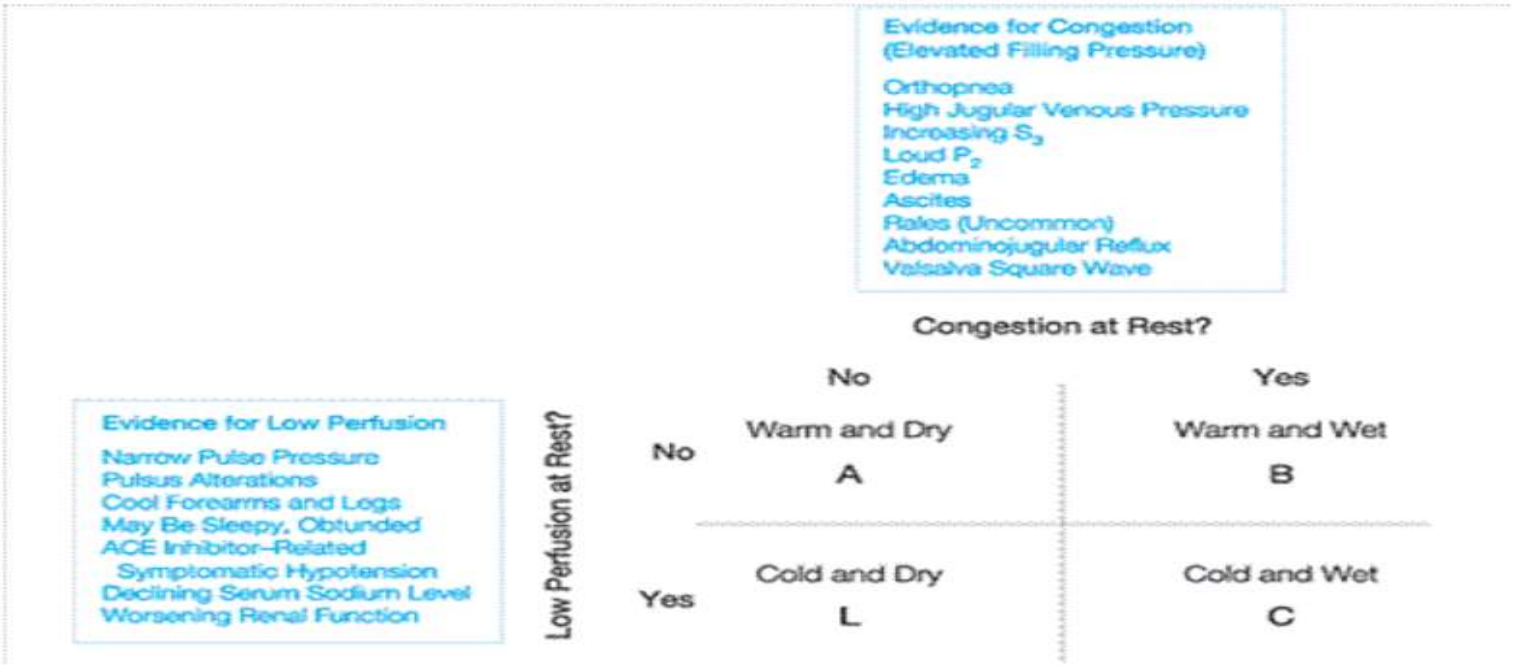
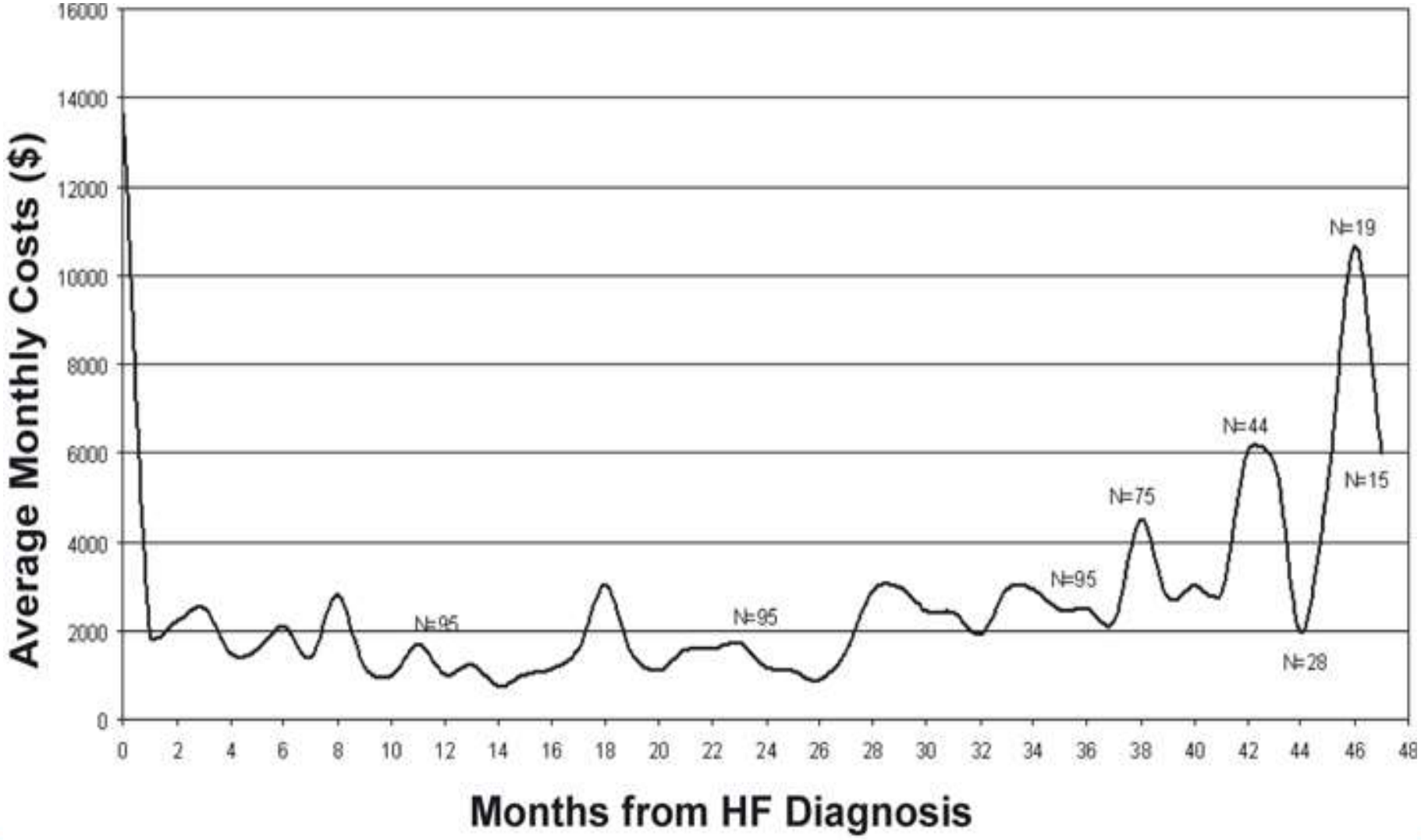


Diagram indicating 2 × 2 table of hemodynamic profiles for patients presenting with heart failure. Most patients can be classified in a 2-minute bedside assessment according to the signs and symptoms shown although in practice some patients may be on the border between the warm-and-wet and cold-and-wet profiles. This classification helps guide initial therapy and prognosis for patients presenting with advanced heart failure. Although most patients presenting with hypoperfusion also have elevated filling pressures (cold and wet profile), many patients present with elevated filling pressures without major reduction in perfusion (warm and wet profile). Patients presenting with symptoms of heart failure at rest or minimal exertion without clinical evidence of elevated filling pressures or hypoperfusion (warm and dry profile) should be carefully evaluated to determine whether their symptoms result from heart failure. Reprinted with permission from Dr Stevenson.

Who Has Advanced Heart Failure? Definition and Epidemiology



Congestive Heart Failure
Volume 17, Issue 4, pages 160-168, 21 JUL 2011 DOI: 10.1111/j.1751-7133.2011.00246.x
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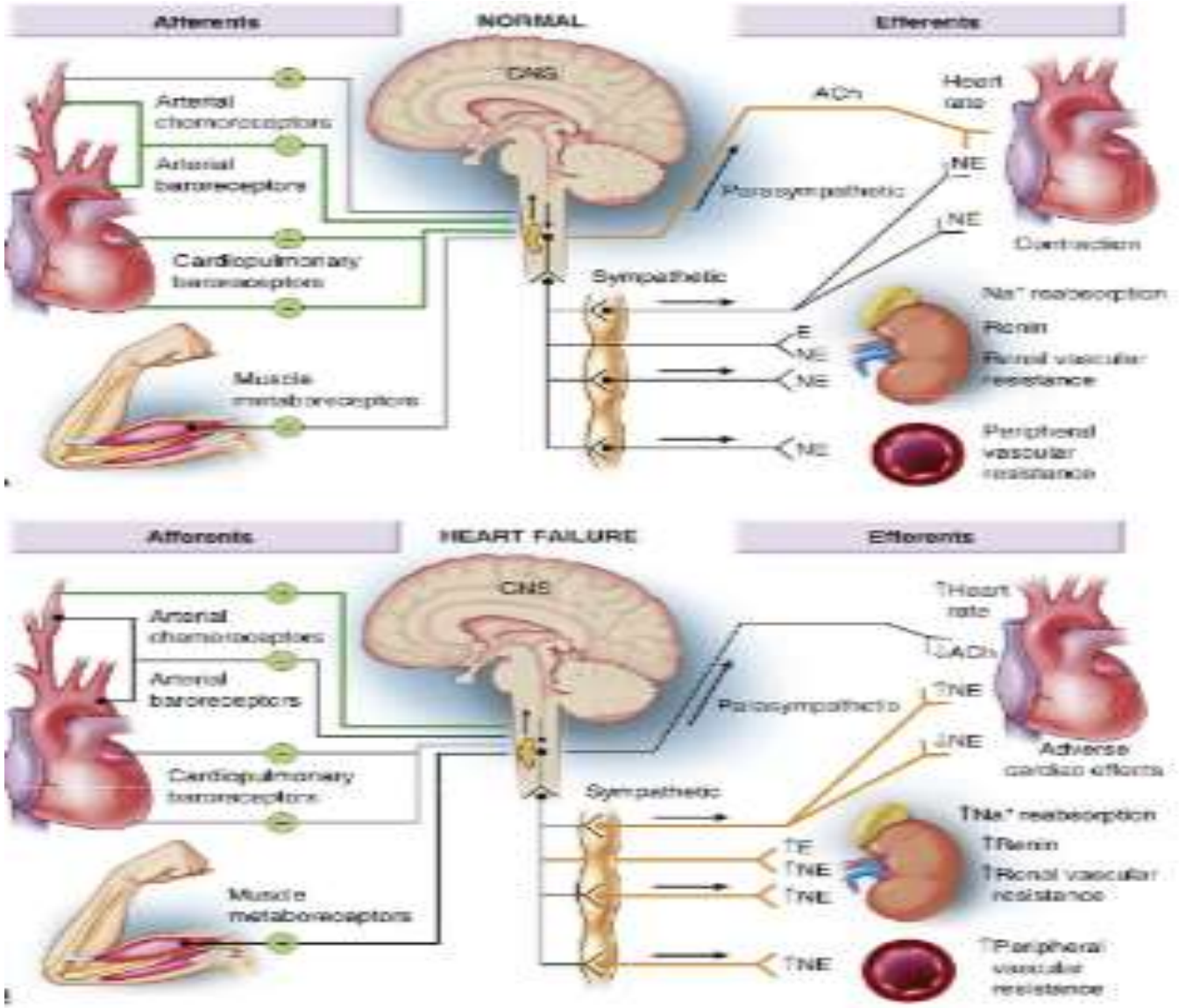
Afferents
NORMAL
Efferents
CNS
Arterial chemoreceptors
Arterial baroreceptors
Cardiopulmonary baroreceptors
Muscle metaboreceptors
ACh
Heart rate
NE
Parasympathetic
Contraction
Sympathetic
E
Na+ reabsorption
Renin
Renal vascular resistance
Peripheral vascular resistance
Afferents
HEART FAILURE
Efferents
CNS
Arterial chemoreceptors
Arterial baroreceptors
Cardiopulmonary baroreceptors
Muscle metaboreceptors
↑Heart rate
↑ACh
↑NE
↓NE
Parasympathetic
Adverse cardiac effects
Sympathetic
↑E
↑NE
↑Na+ reabsorption
↑Renin
↑Renal vascular resistance
↑Peripheral vascular resistance

FORT HAMILTON Hospital
KETTERING HEALTH NETWORK

KETTERING Physician Network
KETTERING HEALTH NETWORK

Virtual Heart Failure Clinic

"Smart" HF management

Sateesh Kesari MD FACC

Disclosures

- I have no current or past relationships with commercial entities
- Speaking fees for current program:
  - I have received no speaker's fee for this learning activity
- Acknowledgements: Slides courtesy of
  - Abbott/ST Jude
  - Medtronic
  - Boston Scientific

Scope of the presentation

- Financial and clinical burden of heart failure
- Tele monitoring
- Device monitoring
- Hemodynamic monitoring

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Heart Failure is a Growing Economic Burden

UNITED STATES

HOSPITALIZATIONS AND READMISSIONS	
> 1,100,000 hospitalizations for HF[1]	**> 3,000,000** hospitalizations include HF as a contributor.[2]
~5 days average length of hospital stay[3]	**~25%** all-cause readmission within 30 days; ~50% within 6 months.[4,5]

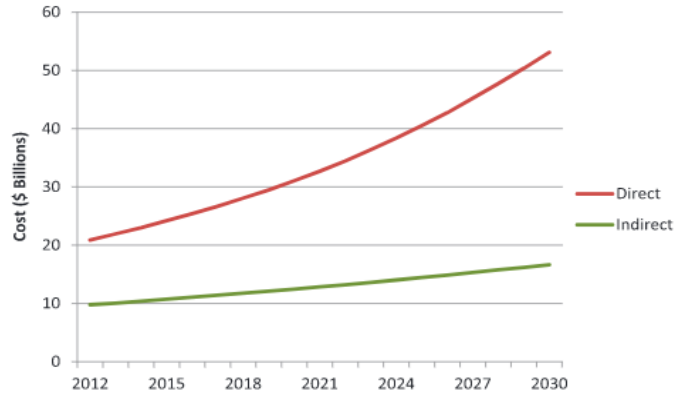


Figure 1. The projected increase in direct and indirect costs attributable to HF from 2012 to 2030 is displayed. Direct costs (cost of medical care) are expected to increase at a faster rate than indirect costs because of lost productivity and early mortality. HF indicates heart failure.

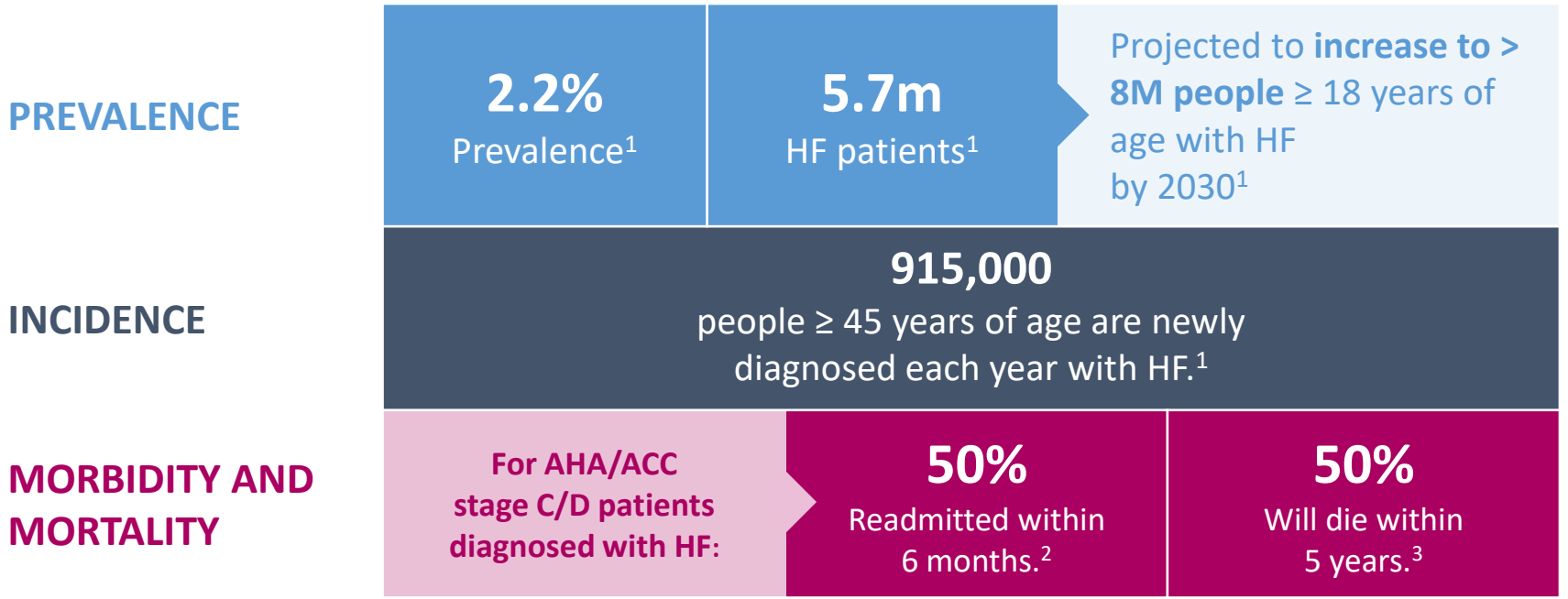
Despite advances in medical therapies to treat heart failure, the hospitalization rate has not changed significantly from 2000. As a result, heart failure continues to be a **MAJOR DRIVER OF OVERALL HEALTH CARE COSTS.**

*Study projections assumes HF prevalence remains constant and continuation of current hospitalization practices

1. CDC NCHS National Hospital Discharge Survey, 2000-10.
2. Bleicker et al. *J Am Coll Cardiol*, 2013.
3. Yancy et al. *J Am Coll Cardiol*, 2006.
4. Wolor DJ, et al. *Am Heart J*, 2001.
5. Krumholz HM, et al. *Circ Cardiovasc Qual Outcomes*, 2009.
6. Yancy CW, et al. *Circulation*, 2013.

Heart Failure is a Growing Global Clinical Burden

- UNITED STATES



HIGH INCIDENCE, HIGH PREVALENCE, AND POOR PROGNOSIS

despite advances in the treatment of heart failure over the past few decades.

1. AHA 2016 Statistics at a Glance, 2016.
2. Krumholz HM, et al. *Circ Cardiovas Qual Outcomes,* 2009.
3. Heidenreich PA, et al. *Circ Heart Failure,* 2013.

Long-term Mortality Risk Increases with Multiple Hospitalizations

Mortality

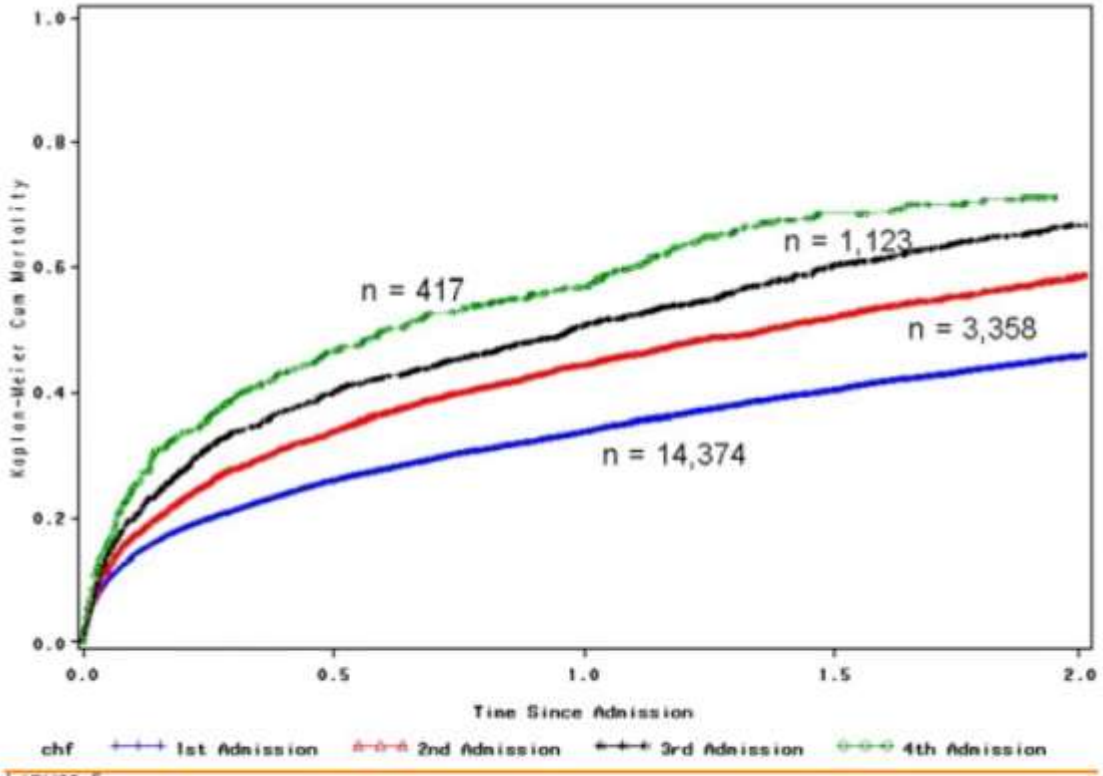


Figure 1

Kaplan-Meier cumulative mortality curve for all-cause mortality after each subsequent hospitalization for HF.

Survival

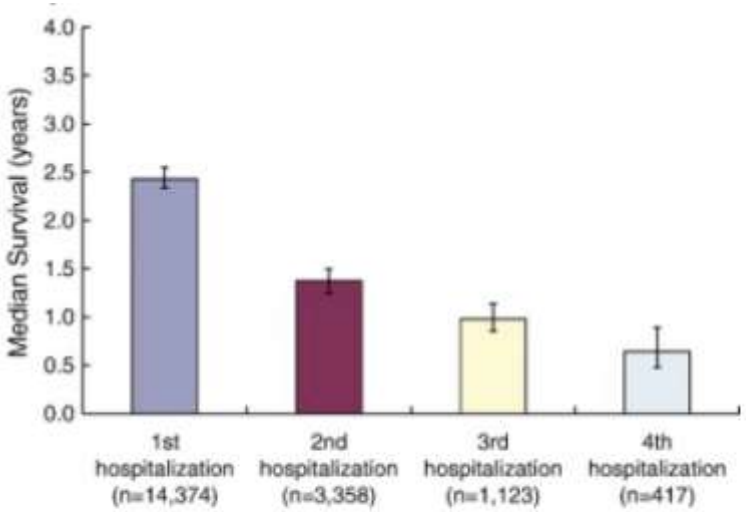


Figure 2

Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.

Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.

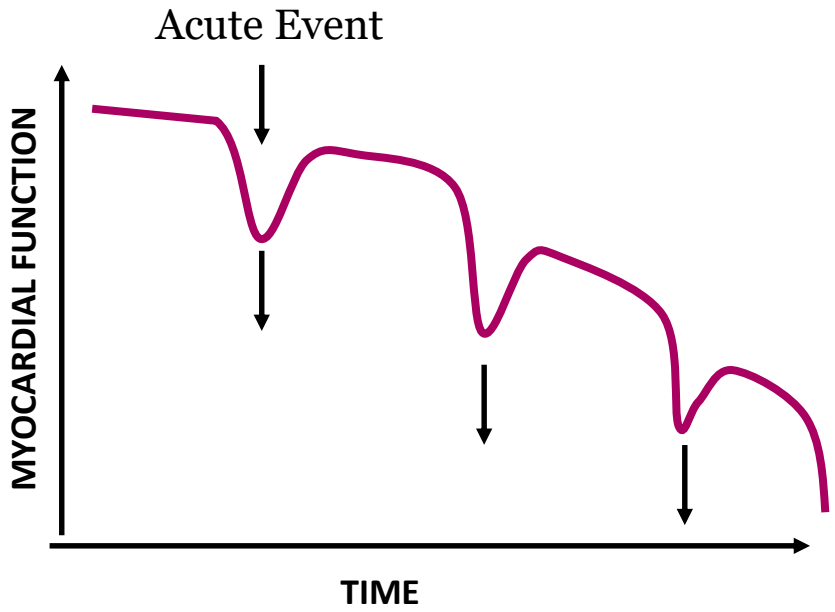
- Setoguchi S, Stevenson LW, Schneeweiss S, *Am Heart J,* 2007;154:260-264.

Goal of Heart Failure Management:

SLOW DISEASE PROGRESSION BY PREVENTING DECOMPENSATION

- EACH EVENT ACCELERATES DOWNWARD SPIRAL OF MYOCARDIAL FUNCTION

With each subsequent HF-related admission, the patient leaves the hospital with a further decrease in cardiac function.



Gheorghiade MD, et al. *Am J. Cardiol*, 2005.

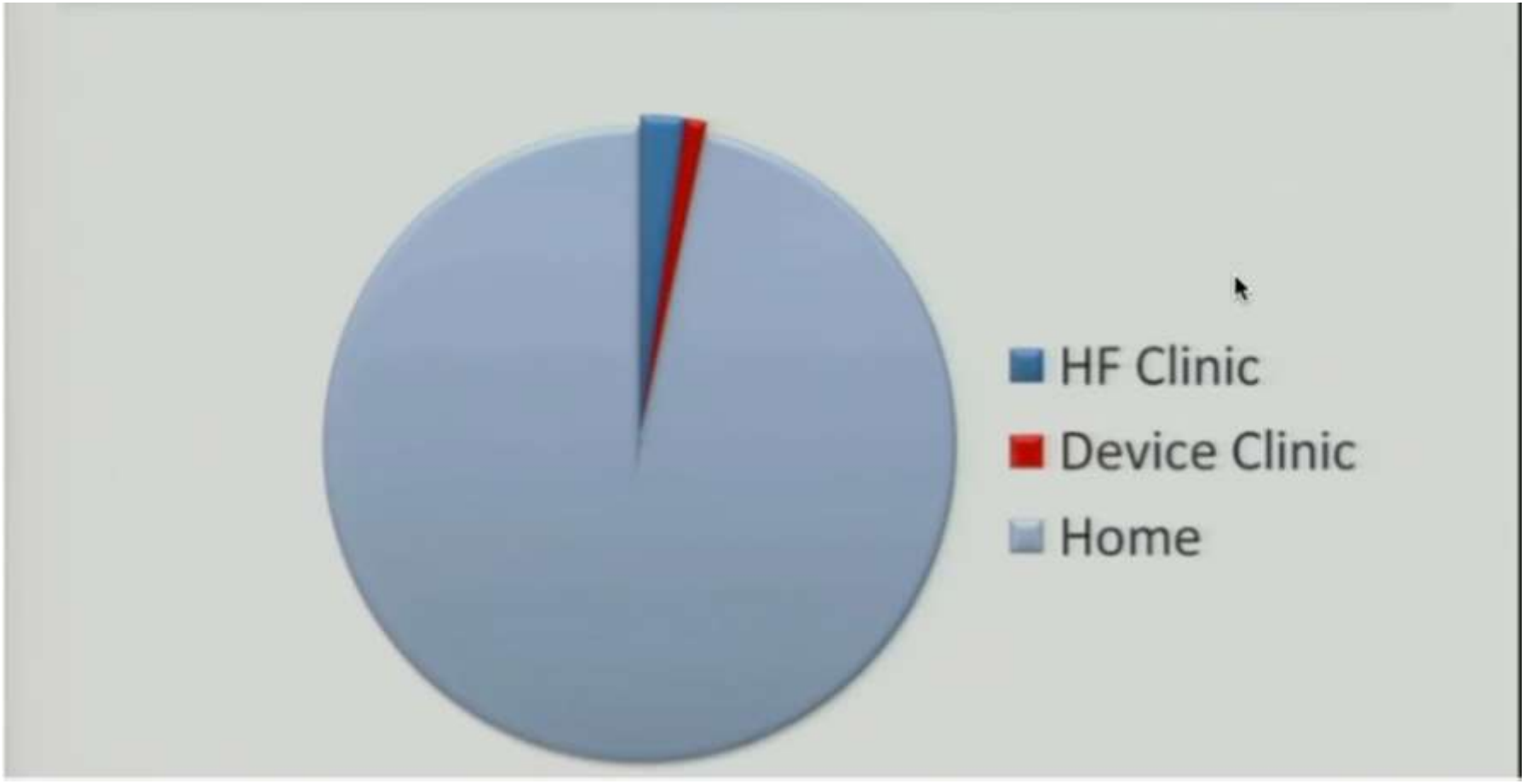
THE GOAL:
Maintain fluid volume to avoid acute decompensation and hospitalization

HF HOSPITALIZATION
is a valid endpoint for measuring decompensation

Scope of the presentation

- Financial and clinical burden of heart failure
- Tele monitoring
- Device monitoring
- Hemodynamic monitoring

Monitored days of a HF patient.



Lynn Stevenson et al

Parameters

- **Daily Impedence**
- **Heart rate variability**
- **Patient Activity**
- **Biventricular pacing < 90%**

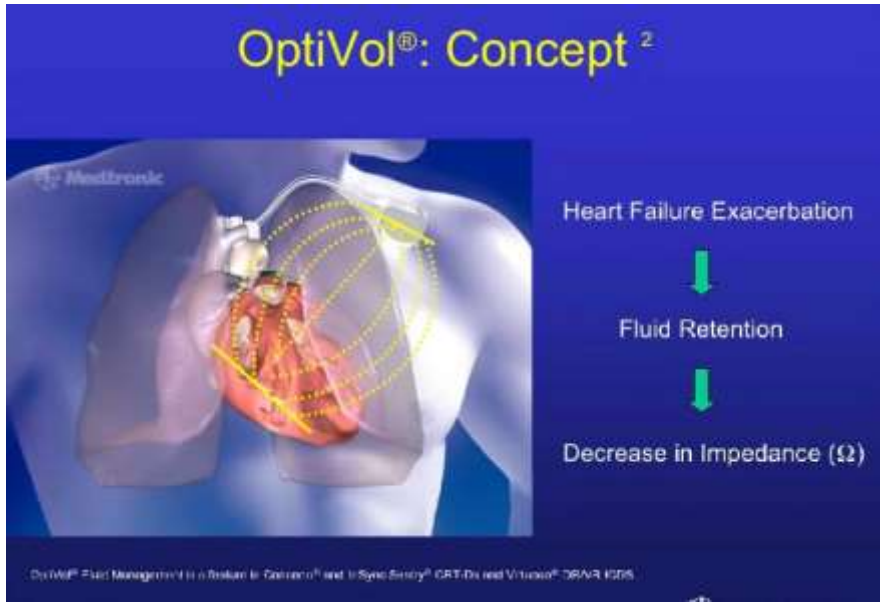
- **Ventricular pacing (ICD)**
- **Night time HR**
- **Atrial fibrillation/AT/AFL**
- **Ventricular tachycardia/ICD shocks**

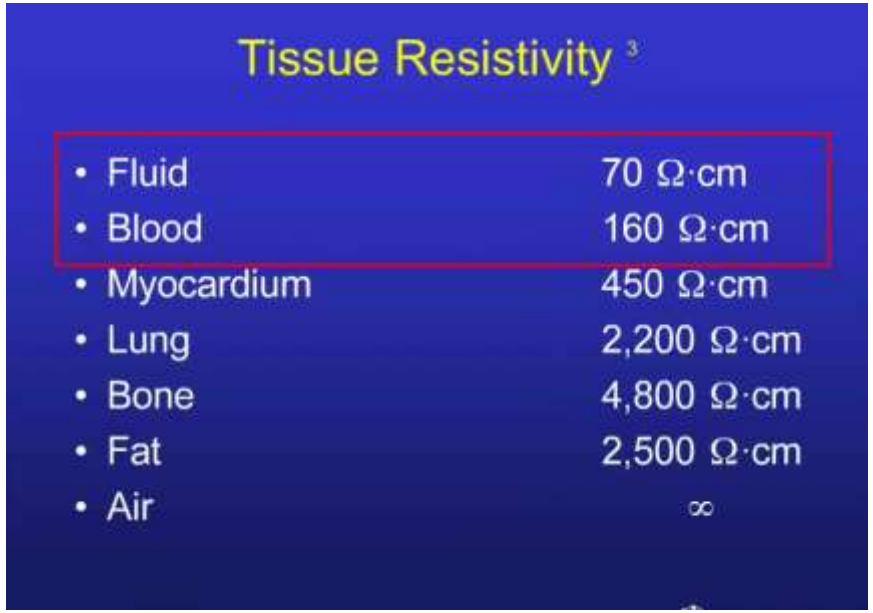
Remote monitoring HF trials

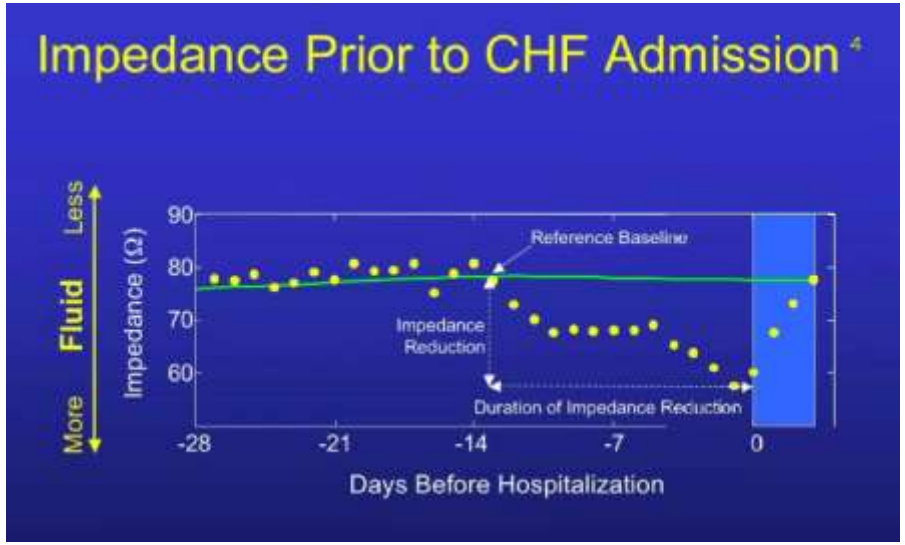
TRIAL	N	PARAMETER MONITORED	IMPACT ON HF HOSPITALIZATION	JOURNAL
TELE-HF[1]	1,653	Signs/symptoms, daily weights	None	*The New England Journal of Medicine, 2010*
TIM-HF[2]	710	Signs/symptoms, daily weights	None	*Circulation, 2011*
TEN-HMS[3]	426	Signs/symptoms, daily weights, BP, nurse telephone support	None	*Journal of the American College of Cardiology, 2005*
BEAT-HF[4]	1,437	Signs/symptoms, daily weights, nurse communications	None	*American Heart Association, 2016*
INH[5]	715	Signs/symptoms, telemonitoring, nurse coordinated DM	None	*Circulation Heart Failure, 2012*
DOT-HF[6]	335	Intrathoracic impedance with patient alert	Increased	*Circulation, 2011*
Optilink[7]	1,002	Intrathoracic impedance	None	*European Journal of Heart Failure, 2011*
REM-HF[8]	1,650	Remote monitoring via ICD, CRT-D or CRT-P	None	*European Society of Cardiology, 2017*
MORE CARE[9]	865	Remote monitoring of advanced diagnostics via CRT-D	None	*European Journal of Heart Failure, 2016*
Total	8,793	**MULTIPLE TRIALS, > 8,500 PATIENTS:** No reduction in HF hospitalization		

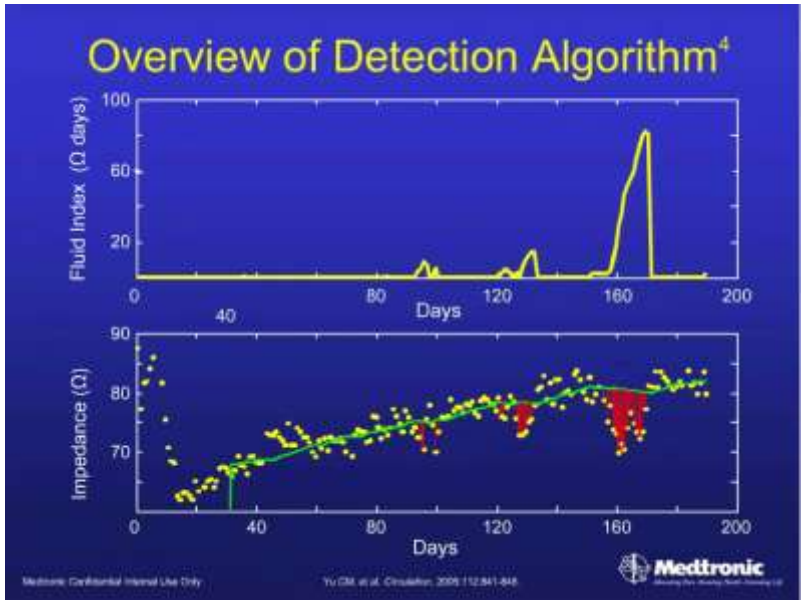
- 1. Chaudhry SI, et al. *N Engl J Med*, 2010.
- 2. Koehler F, et al. *Circulation*, 2011.
- 3. Cleland JG, et al. *J Am Coll Cardiol*, 2005.
- 4. Ong MK, et al. *JAMA Intern Med*, 2016.
- 5. Angermann DE, et al. *Circ Heart Fail*, 2012.
- 6. van Veldhuisen DJ, et al. *Circulation*, 2011.
- 7. Brachmann J, et al. *Eur J Heart Fail*, 2011.
- 8. Cowie MR, *ESC*, 2016.
- 9. Boriani G, et al. *Eur J Heart Fail*, 2016.

Impedence

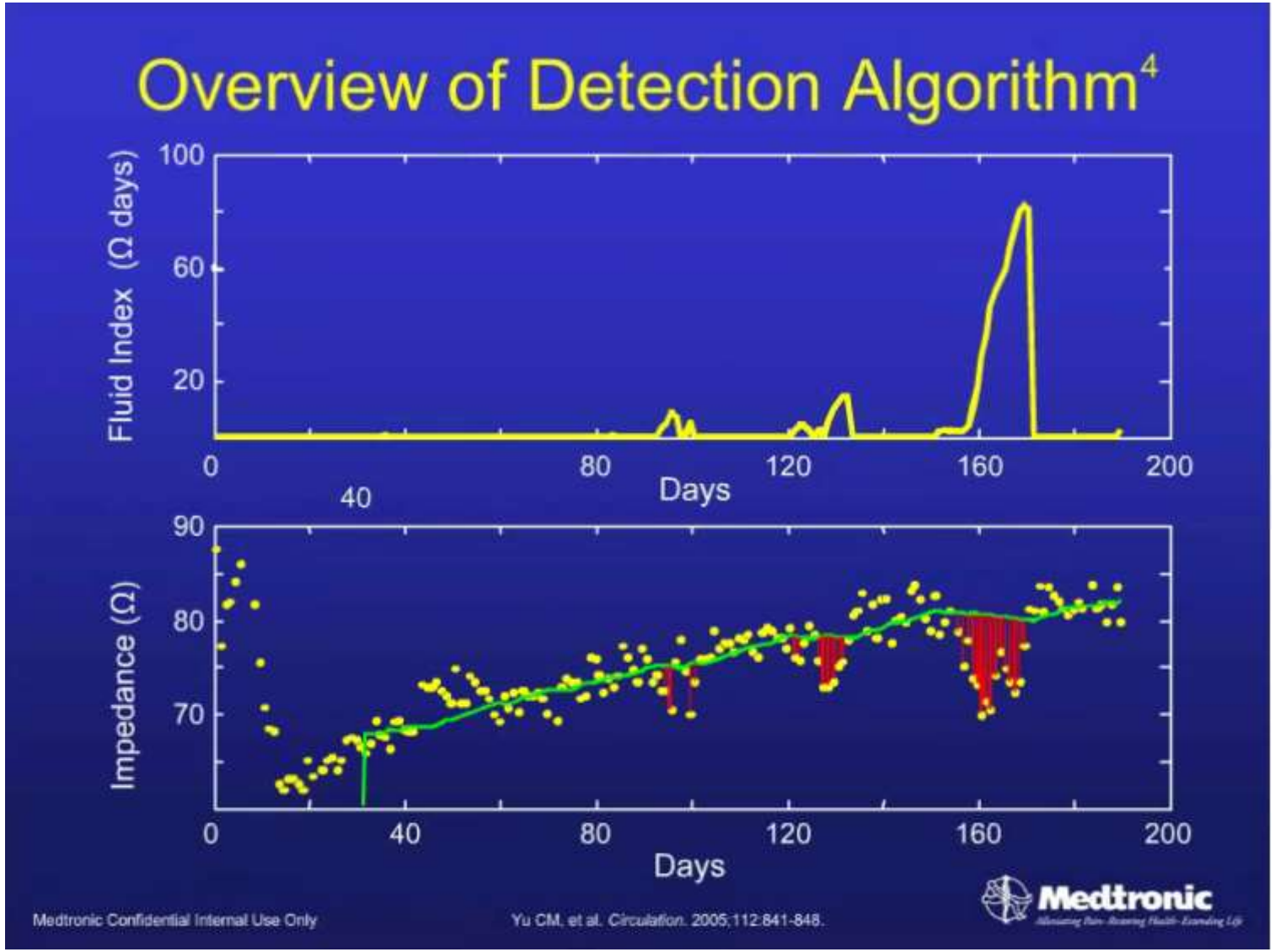

OptiVol®: Concept [2]
Heart Failure Exacerbation
Fluid Retention
Decrease in Impedance (Ω)


Tissue Resistivity [3]
• Fluid 70 Ω·cm
• Blood 160 Ω·cm
• Myocardium 450 Ω·cm
• Lung 2,200 Ω·cm
• Bone 4,800 Ω·cm
• Fat 2,500 Ω·cm
• Air ∞


Impedance Prior to CHF Admission [4]
More Fluid Less
Impedance (Ω)
90
80
70
60
Reference Baseline
Impedance Reduction
Duration of Impedance Reduction
-28
-21
-14
-7
0
Days Before Hospitalization

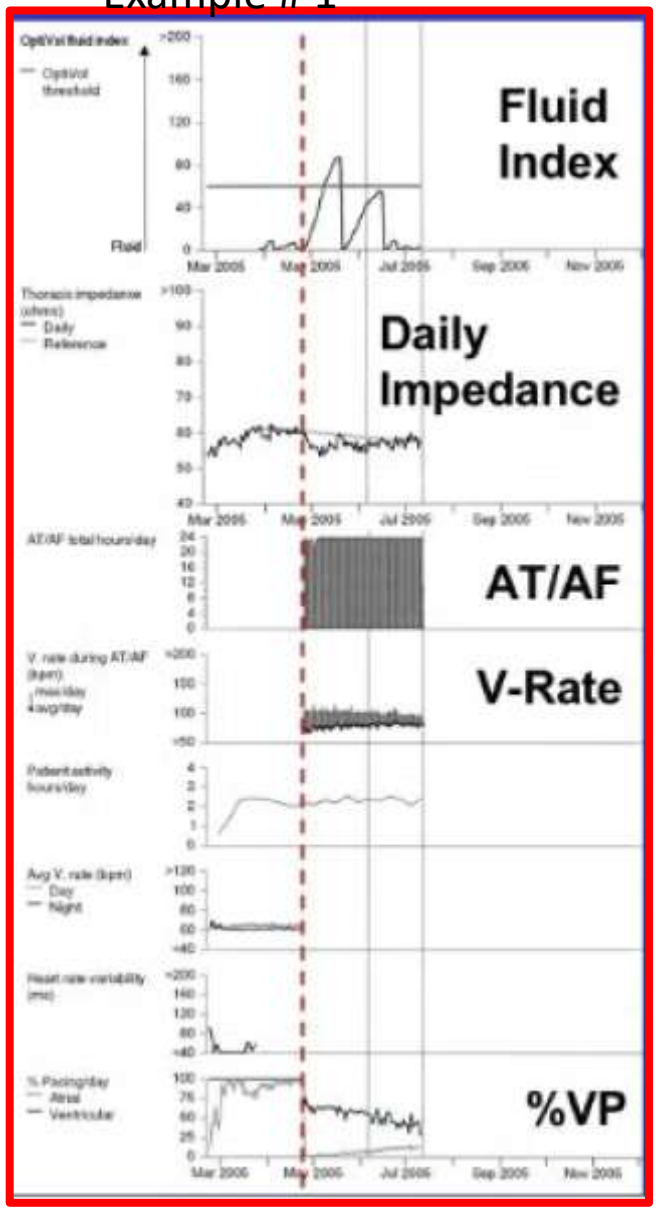

Overview of Detection Algorithm[4]
Fluid Index (Ω days)
100
60
20
0
40
80
120
160
200
Days
Impedance (Ω)
90
80
70
0
40
80
120
160
200
Days
Medtronic

Impedence


Overview of Detection Algorithm[4]
Fluid Index (Ω days)
100
60
20
0
80
120
160
200
Days
40
Impedance (Ω)
90
80
70
0
40
80
120
160
200
Days
Medtronic Confidential Internal Use Only
Yu CM, et al. Circulation. 2005;112:841-848.
Medtronic

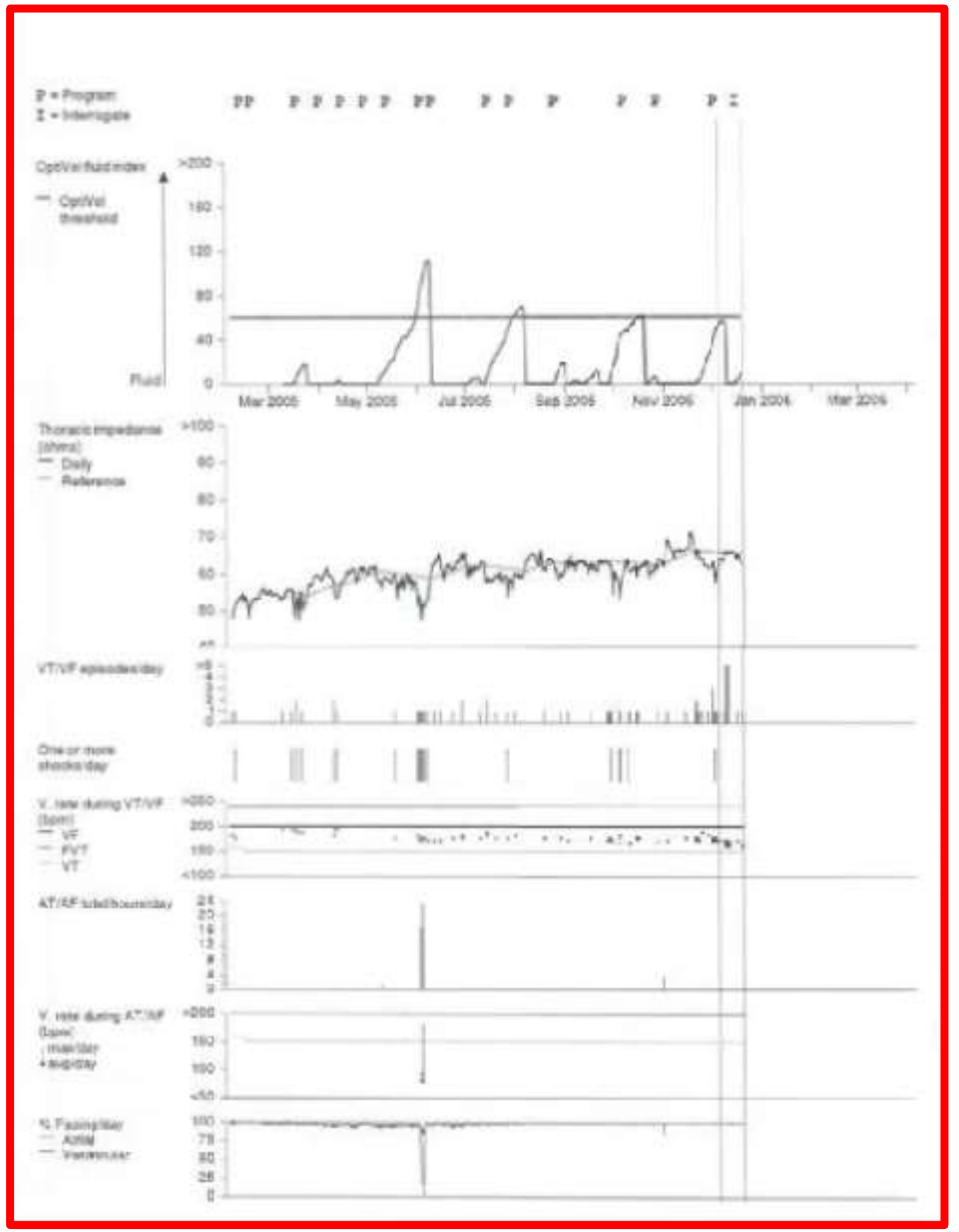
Impedence cases

Example # 1



-Drop in Impedence
-Preceded by AT/AF
-High Ventricular rates
-Loss of CRT pacing

Example # 2



-Drop in impedence
-followed by VT storm

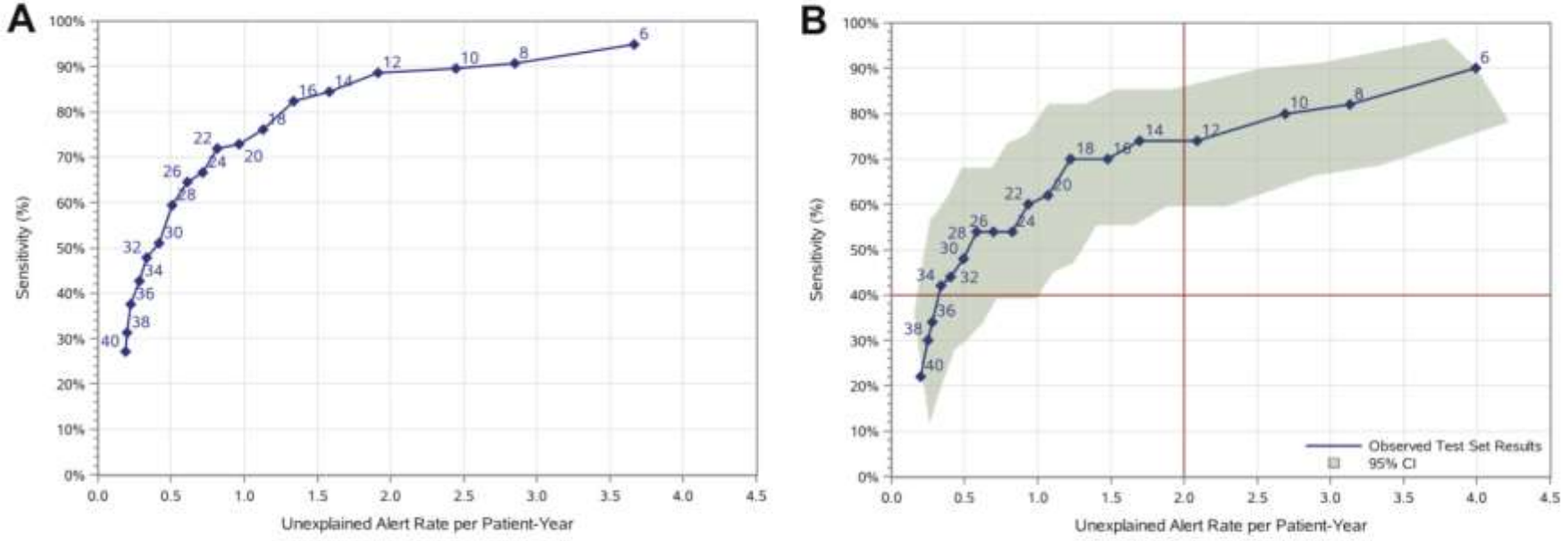
Device monitoring with multiple paramaters

- Heart Logic
  - Multisense trial
  - Manage HF trial

- Beacon HF system
  - Partners HF trial

Multisense trial for HeartLogic

FIGURE 2 Modified Receiver Operating Characteristic Curves Showing the Sensitivity Versus Unexplained Alert Rate for the HeartLogic Index

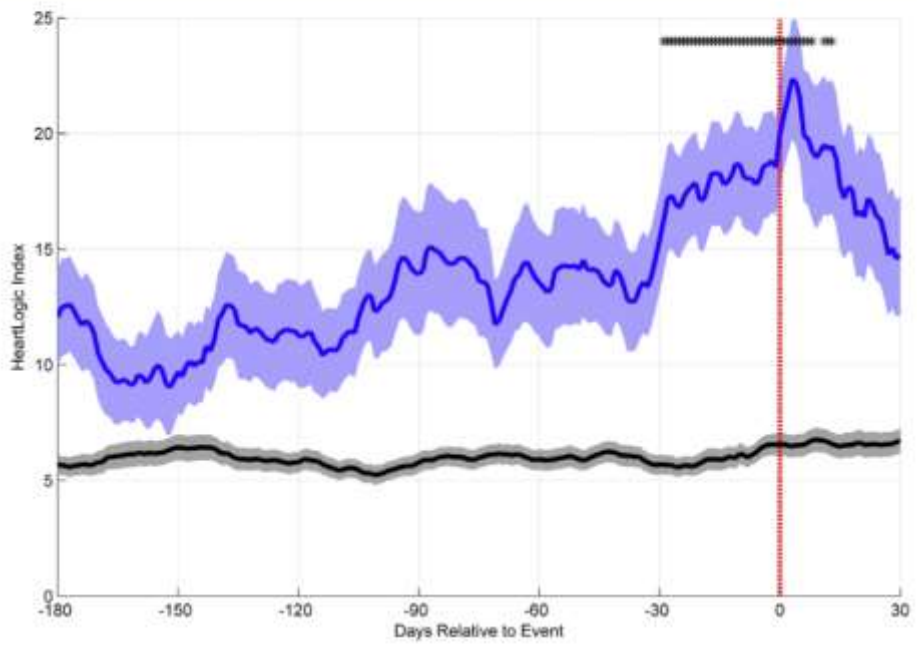


(A) Development Set. **(B)** Test Set. Each **point** corresponds to an alert threshold. The shaded regions represent the 95% confidence interval (CI) of the mean. The **red lines** indicate the pre-specified performance goals.

JACC: Heart Failure vol 5. no. march 2017;216-25

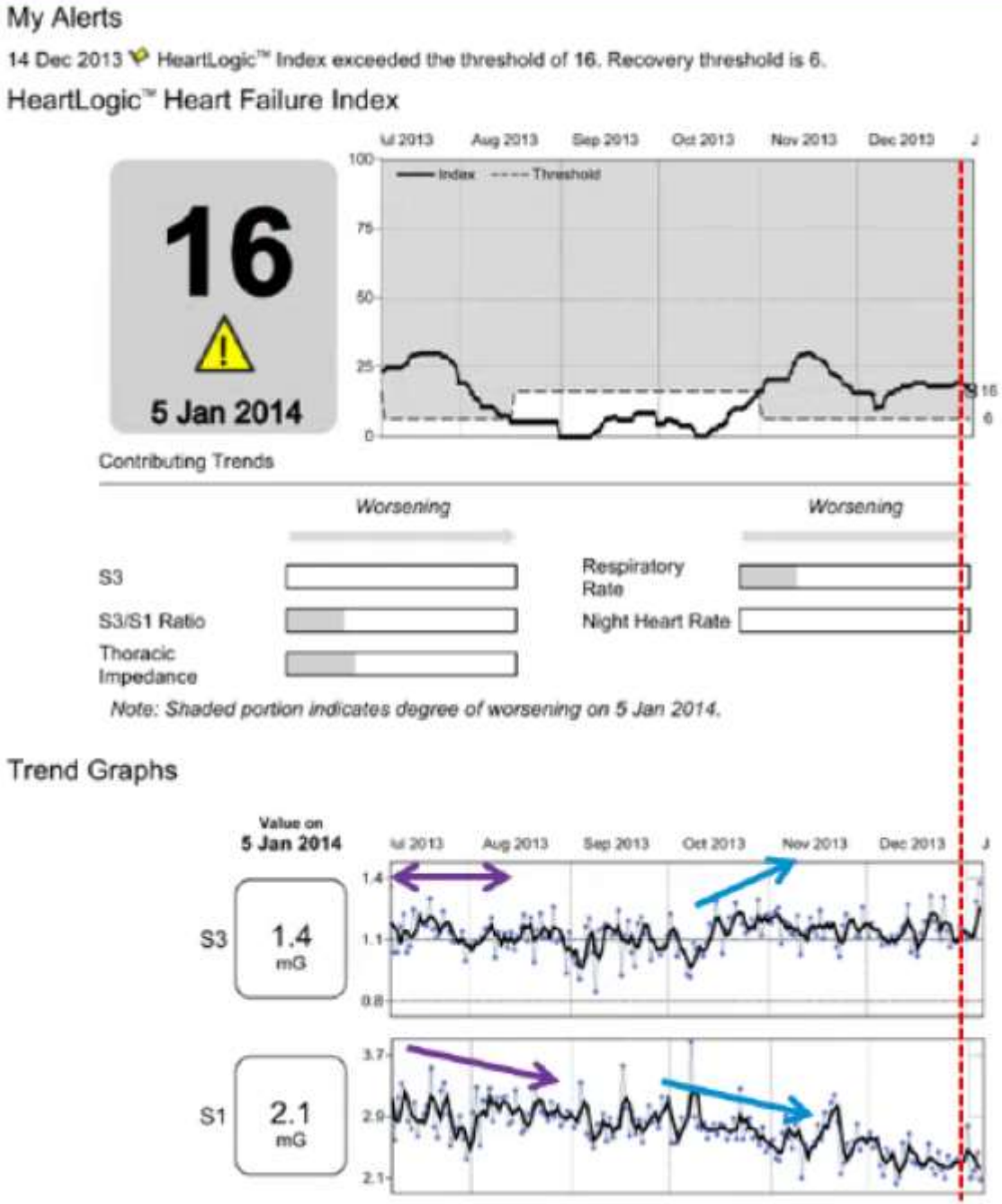
HeartLogic index trend in pts with and without HFE

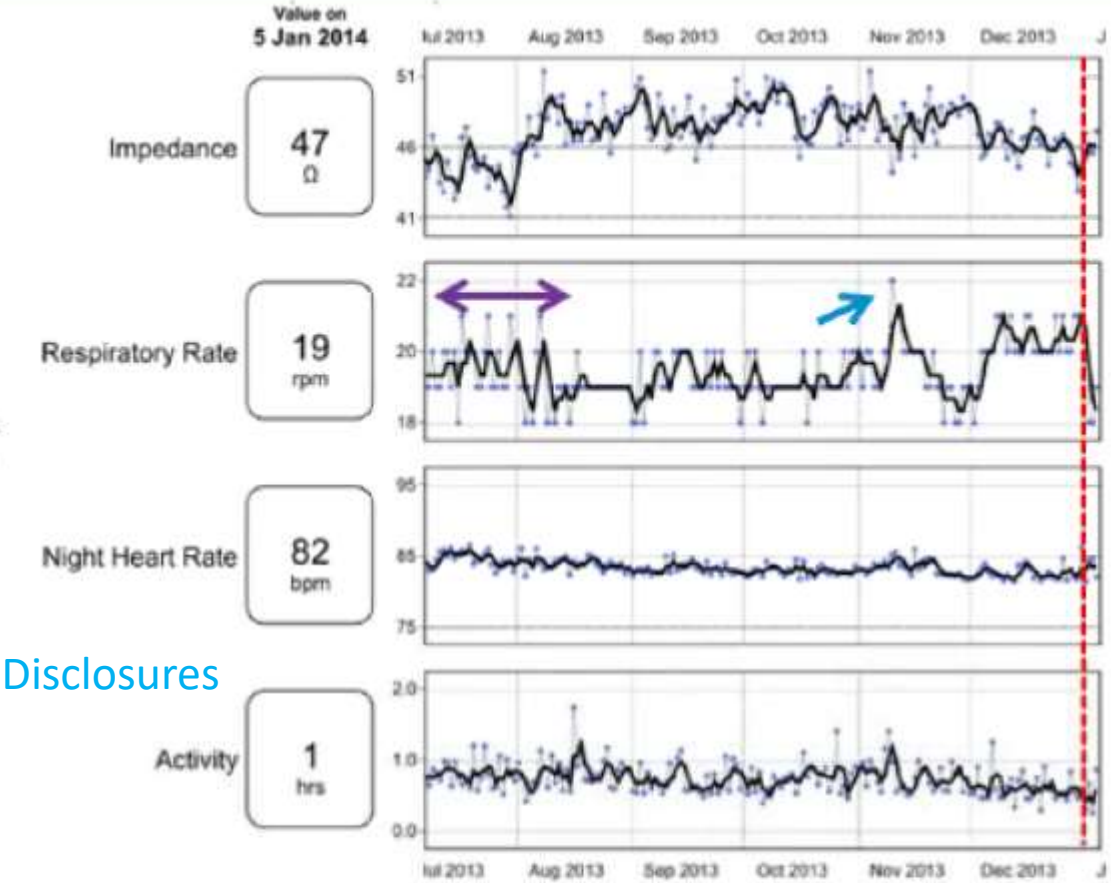
FIGURE 4 Temporal Profile of HeartLogic Index Trends in Patients With and Without Heart Failure Events



Data are displayed as mean ± SEM. The **shaded regions** represent the SEM. HeartLogic index in patients with usable HFE **(blue line)** aligned by the date of the HFE **(vertical line)** at Day 0; HeartLogic index in patients without HFE **(black line)** aligned by the last available HeartLogic index date for each patient (Day 30). Days related to heart failure events (HFEs) with the HeartLogic index are significantly greater ($p < 0.05$, rank sum test) than a 3-month baseline period ending 90 days before the HFE are indicated by **asterisks**.

JACC: Heart Failure vol 5. no. march 2017;216-25





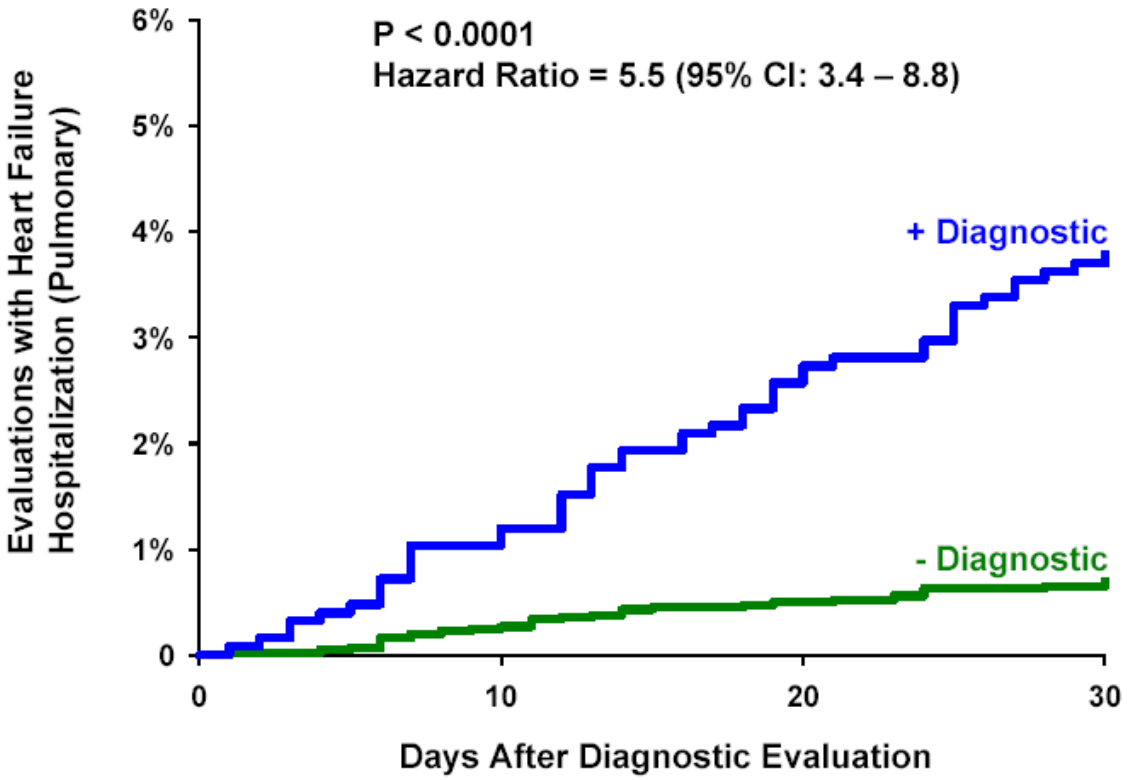
Disclosures

Dec 31, 2013 **HF Hospitalization**

Admitted for exacerbated CHF and treated with IV lasix 40 mg for three days.

PARTNERS-HF: COMBINED DIAGNOSTICS

Partners HF study showed monthly review of HF diagnostic data could have identified patients at higher risk of HF hospitalizations within the subsequent month. OptiVol/HFMR identified patients were 5.5 times as likely to be hospitalized within 30



Whellan DJ, et al. *J Am Coll Cardiol.* 2010;55:1803-1810.

+ Diagnostic

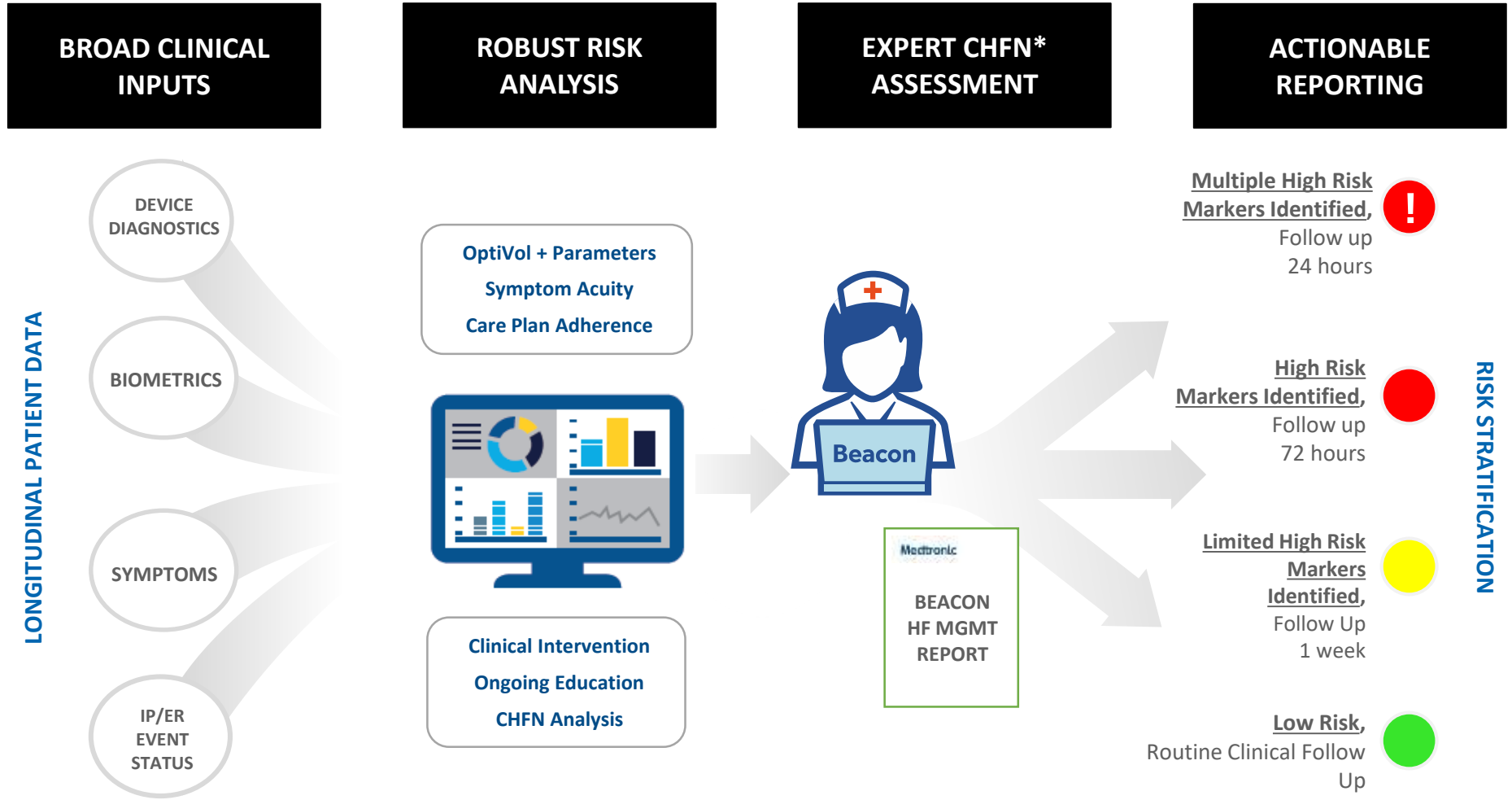
TWO diagnostic criteria met

- ❑ Fluid Index ≥ 100
- ❑ Fluid Index ≥ 60
- ❑ Avg. Activity < 1 hr over 1 week
- ❑ Avg night HR > 85 bpm for 7 consecutive days
- ❑ HRV < 60 ms for 7 consecutive days
- ❑ % V pacing < 90% for 5 of 7 days
- ❑ One or more shocks
- ❑ AF > 6 hrs on at least one day in pts without persistent AF
- ❑ AF > 24 hrs & VR-AF > 90 bpm

N = 694 patients
Monthly Evaluations = 5693
HF Events = 78

TRIAGE

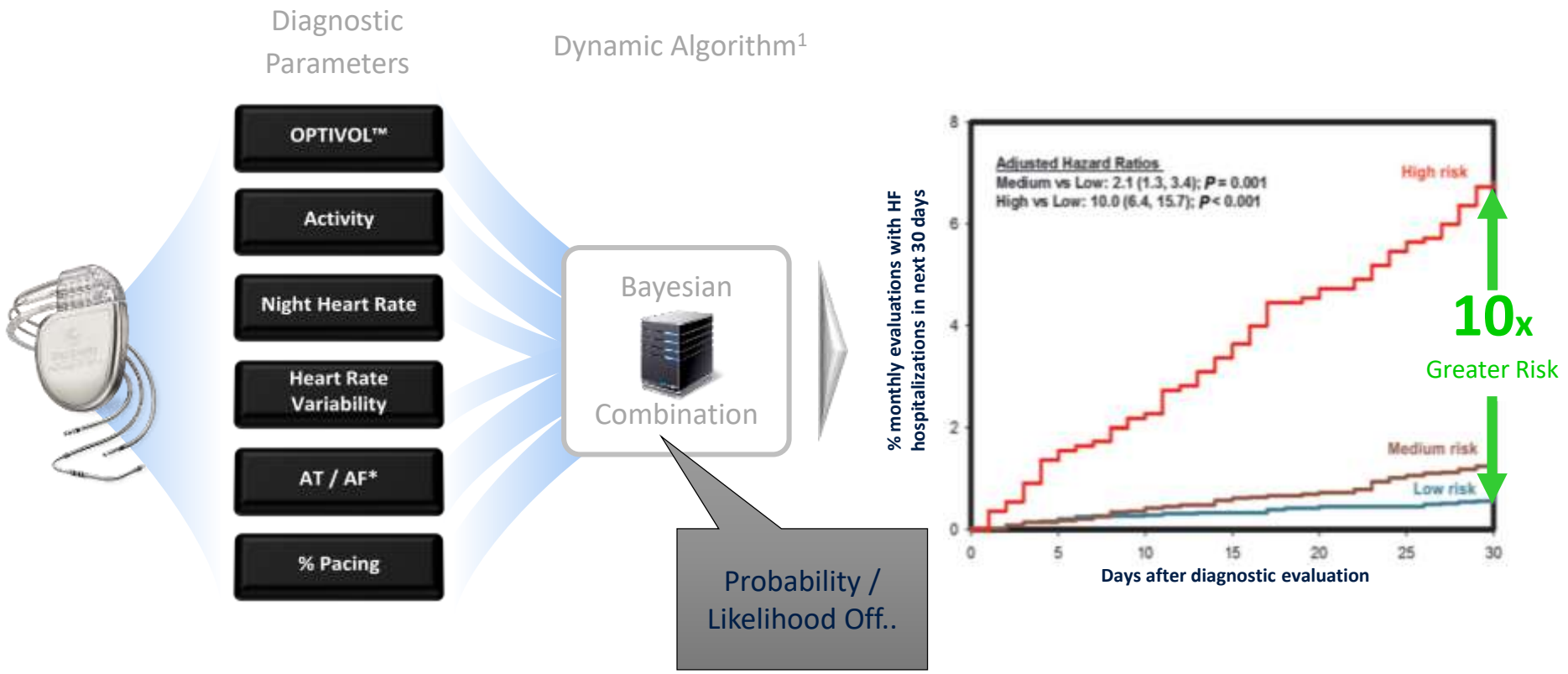
COMBINING DEVICE DIAGNOSTICS & EXTERNAL BIOMETRICS



*Certified Heart Failure Nurse, certified by the American Association of Heart Failure Nurses

Device Diagnostics

COMBINING DYNAMIC DATA TO PROVIDE ADVANCED INSIGHTS



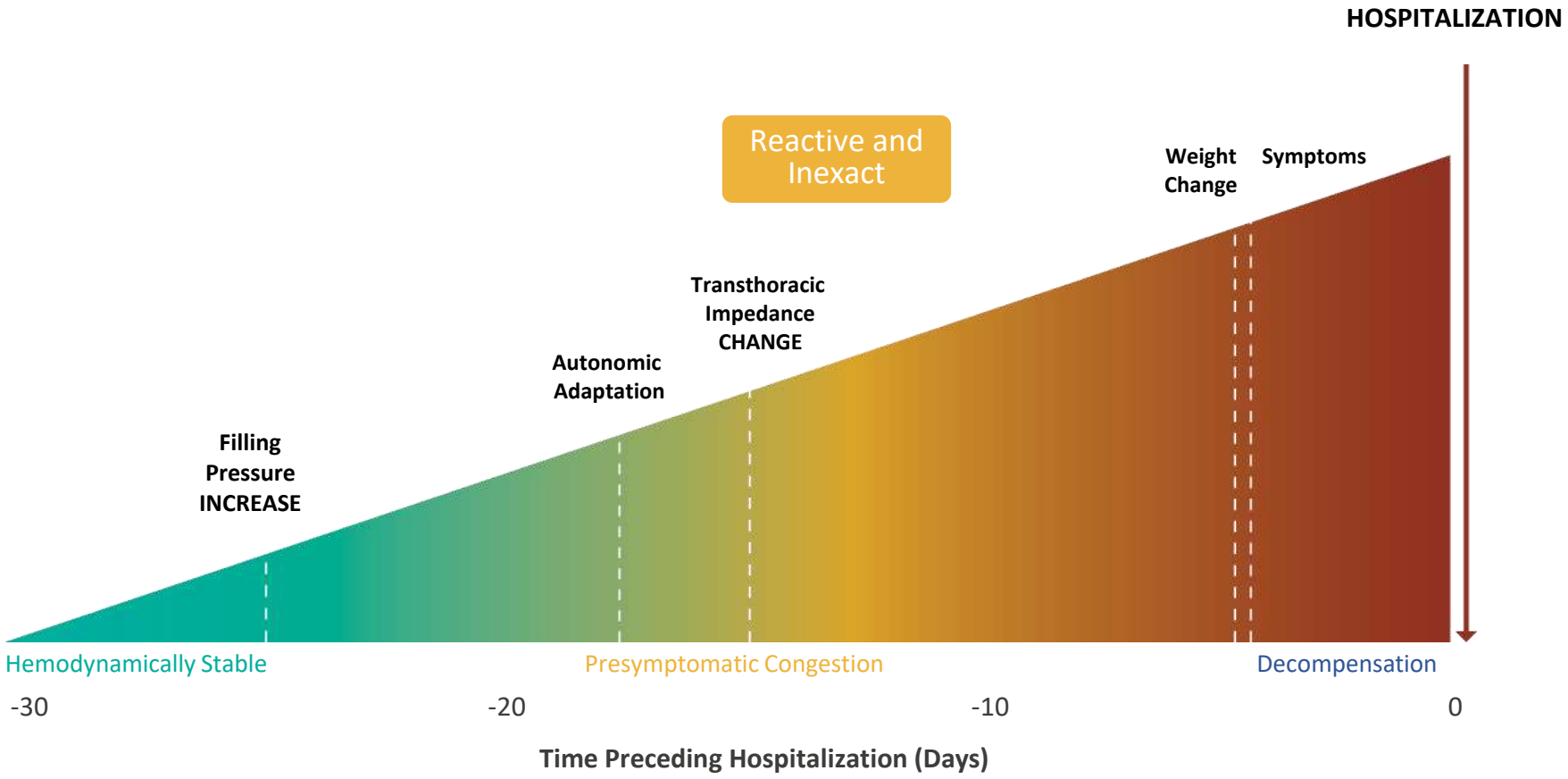
Patients with a high risk score were **10 times** more likely to have a heart failure event in the next 30 days than those with a low risk score[1]

[1] Cowie MR, Sarkar S, Koehler J, et al. Eur Heart J. 2013 Aug;34(31):2472-80

Scope of the presentation

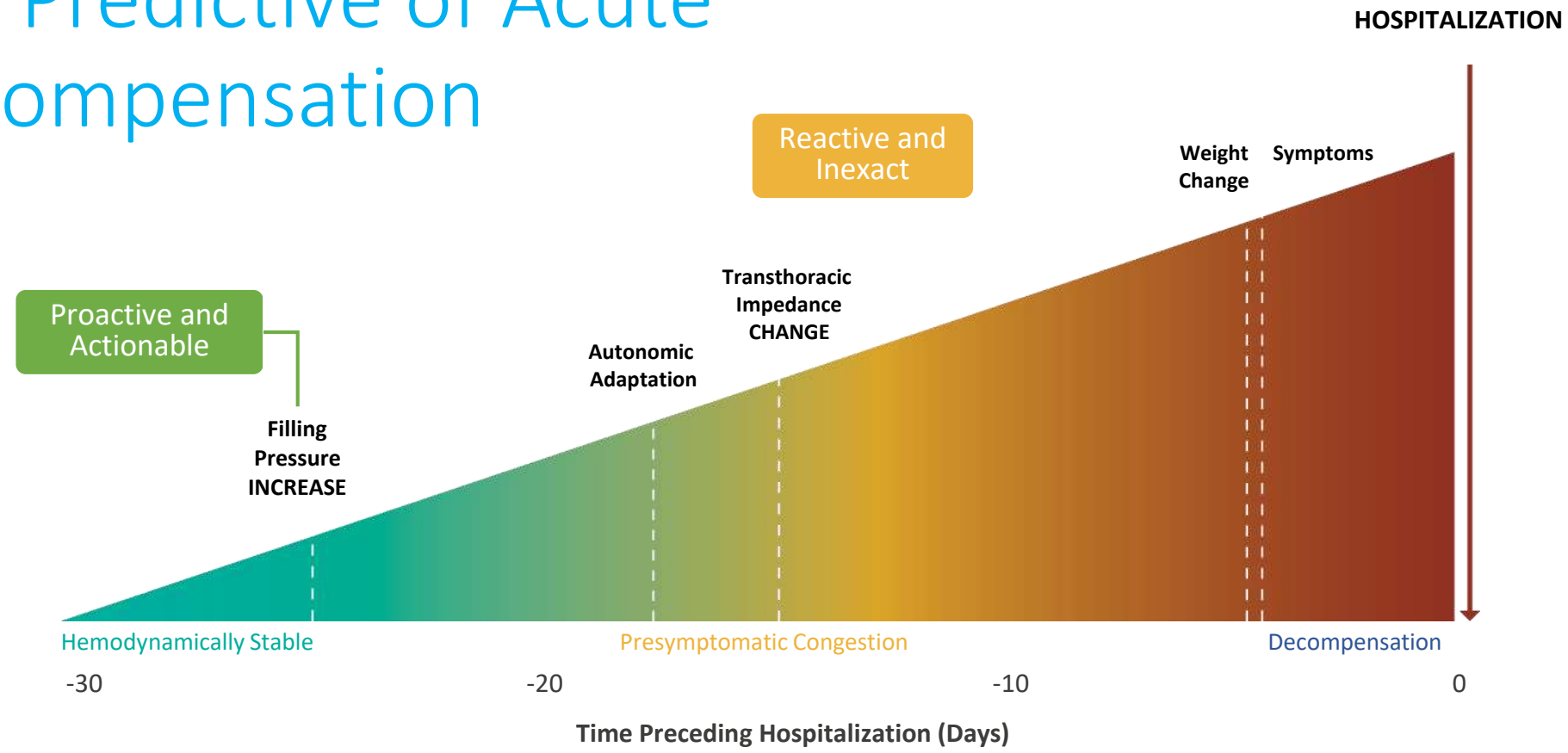
- Burden of heart failure with financial and clinical impact
- Tele monitoring
- Device monitoring
- Hemodynamic monitoring

Current Parameters for Managing HF are Reactive and Inexact



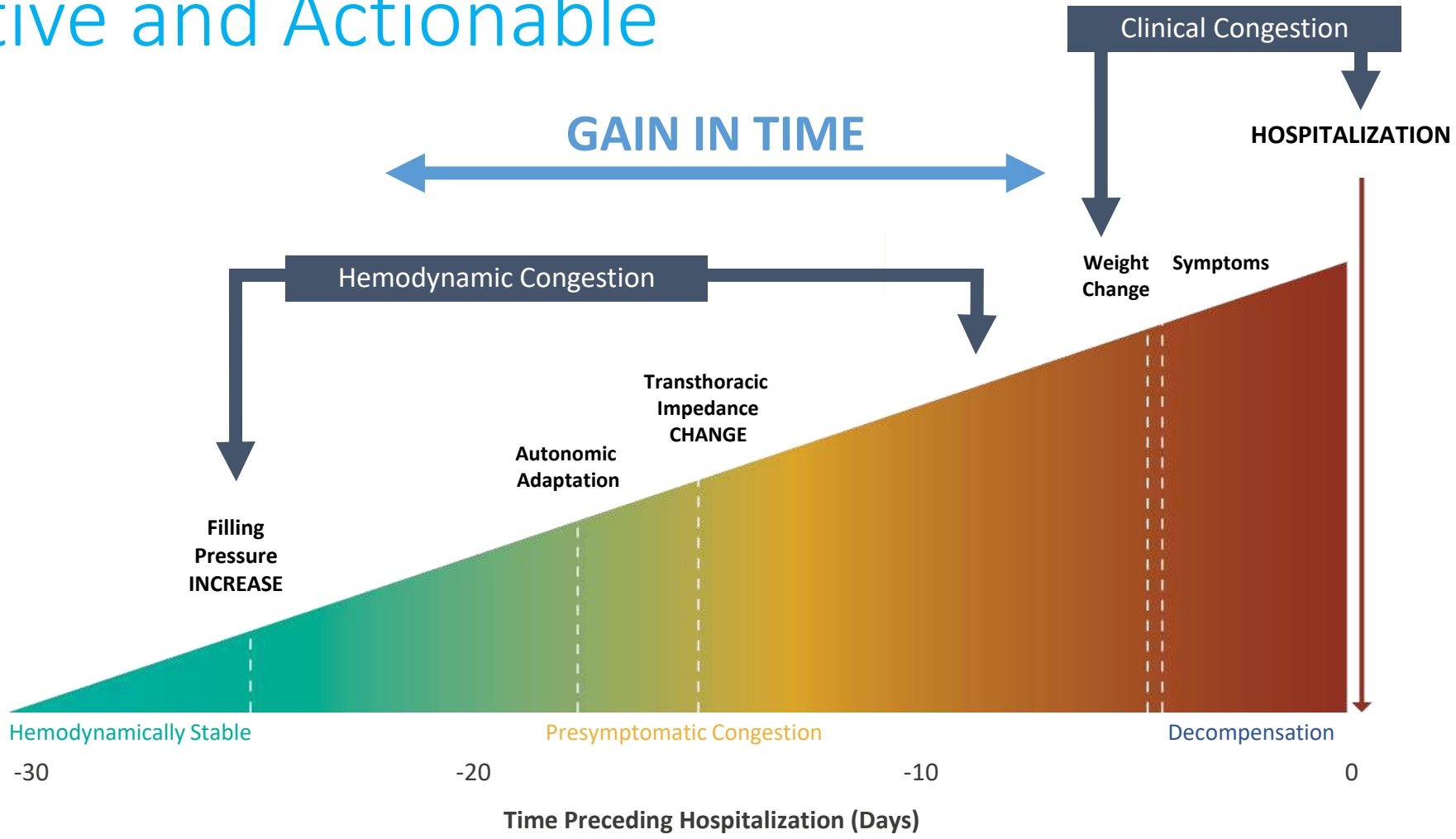
- Adamson PB, et al. *Curr Heart Fail Reports*, 2009.

Monitoring for Increased Filling Pressures is Proactive and Actionable, and Predictive of Acute Decompensation



- Adamson PB, et al. *Curr Heart Fail Reports*, 2009.

Monitoring Pulmonary Artery Pressures, Proactive and Actionable



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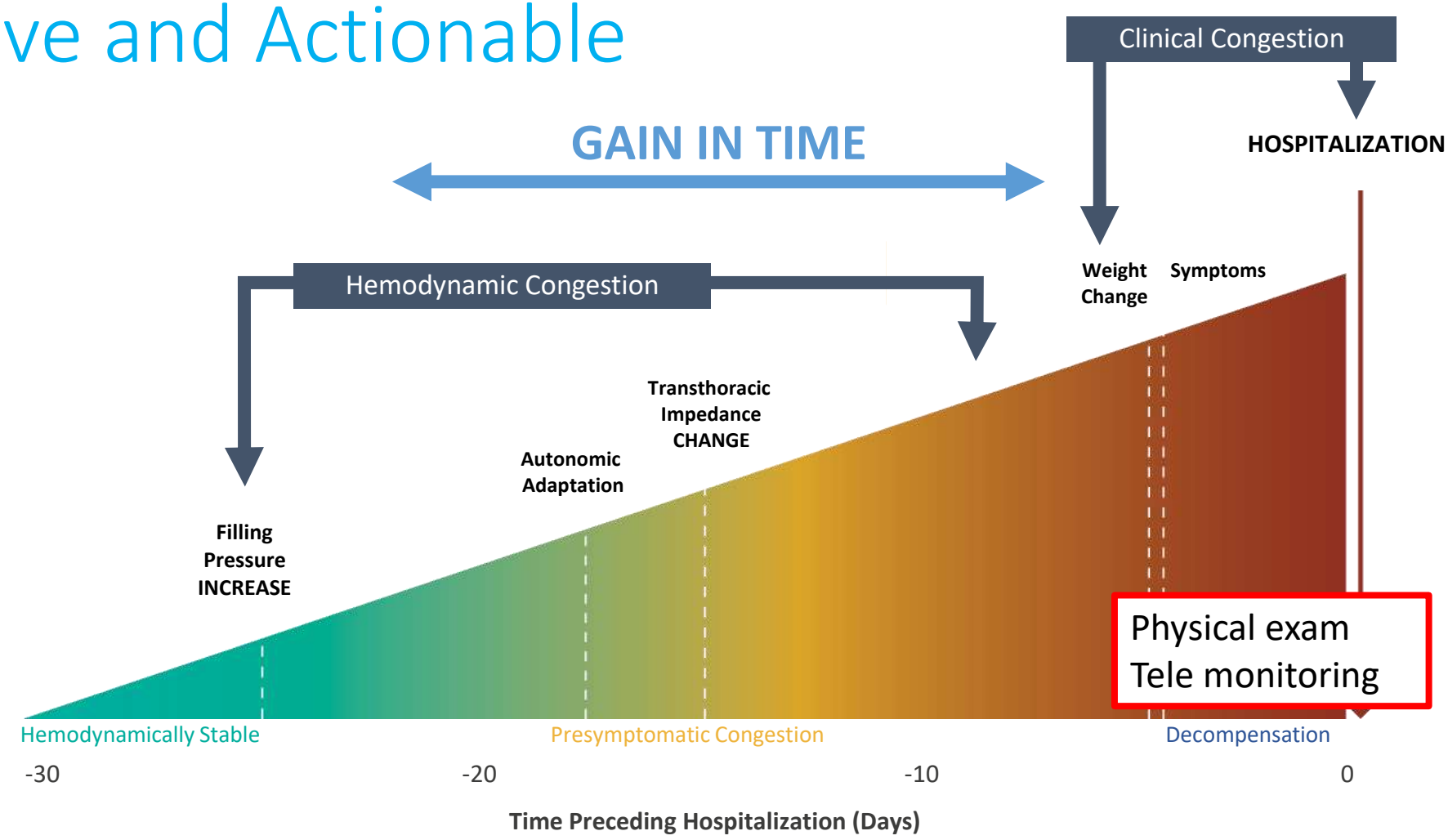
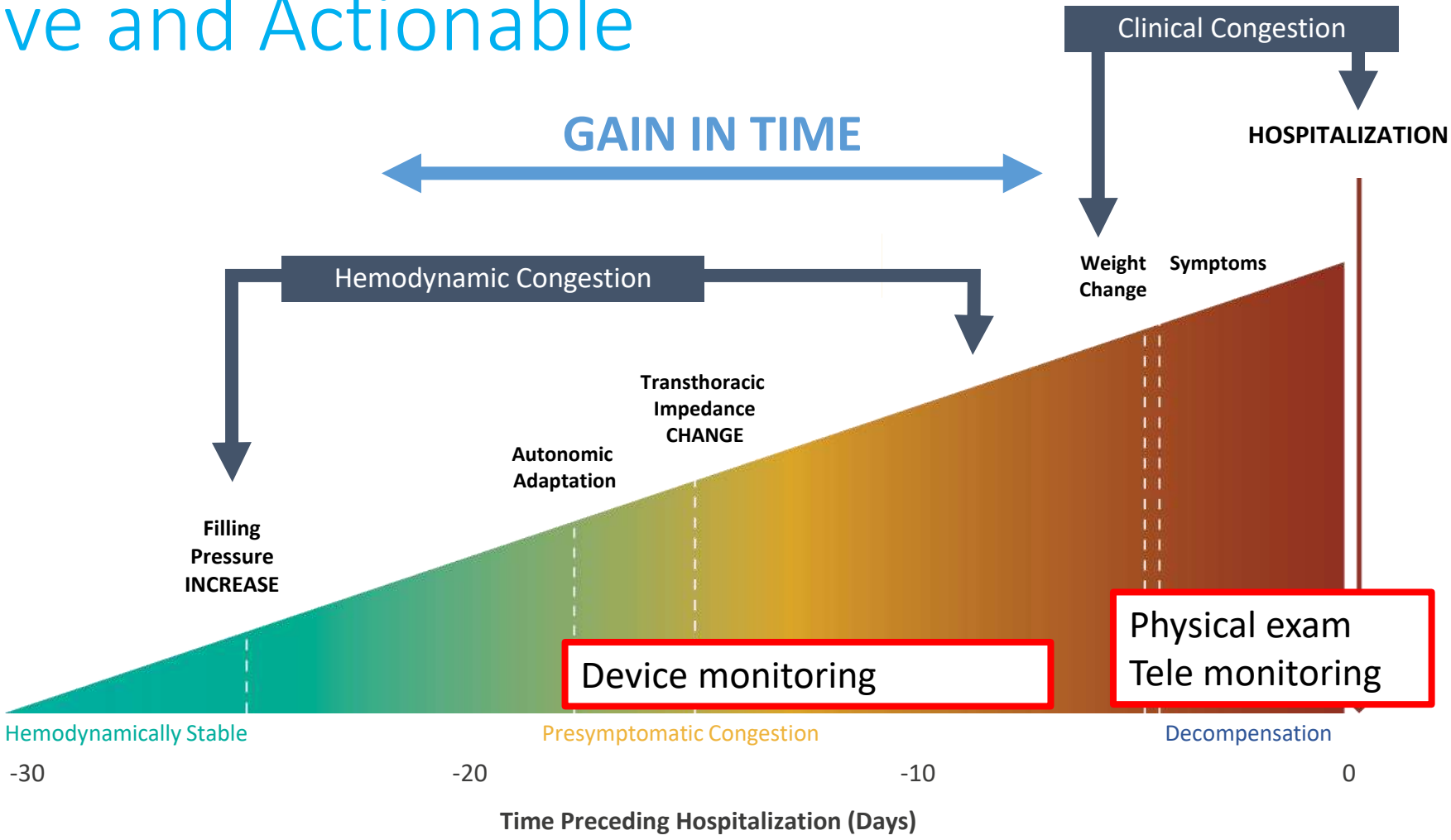
Monitoring Pulmonary Artery Pressures, Proactive and Actionable



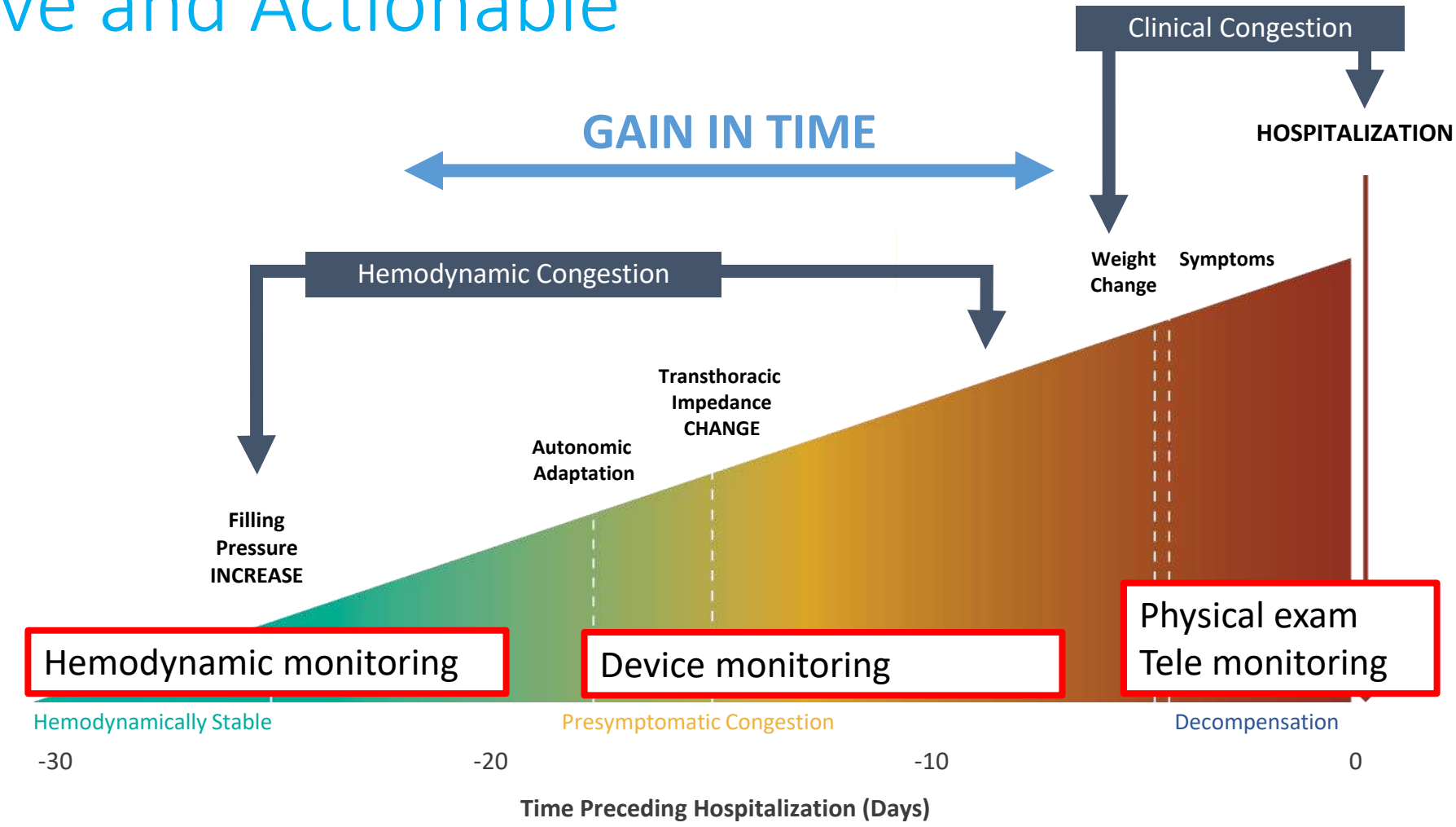
- Adamson PB, et al. *Curr Heart Fail Reports*, 2009.

Monitoring Pulmonary Artery Pressures, Proactive and Actionable



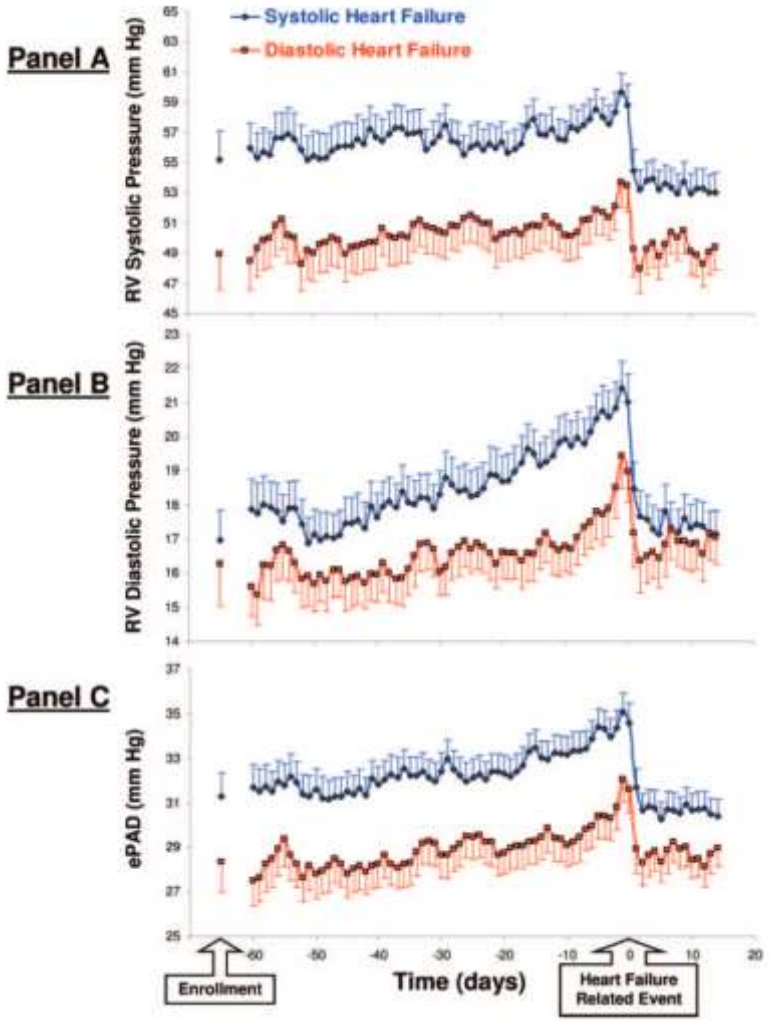
- Adamson PB, et al. *Curr Heart Fail Reports*, 2009.

Monitoring Pulmonary Artery Pressures, Proactive and Actionable



- Adamson PB, et al. *Curr Heart Fail Reports*, 2009.

Intracardiac hemodynamics



Chronicle device

Zile et al, Circulation
. 2008;118:1433-1441.

CardioMEMS™ HF System for the Management of HF

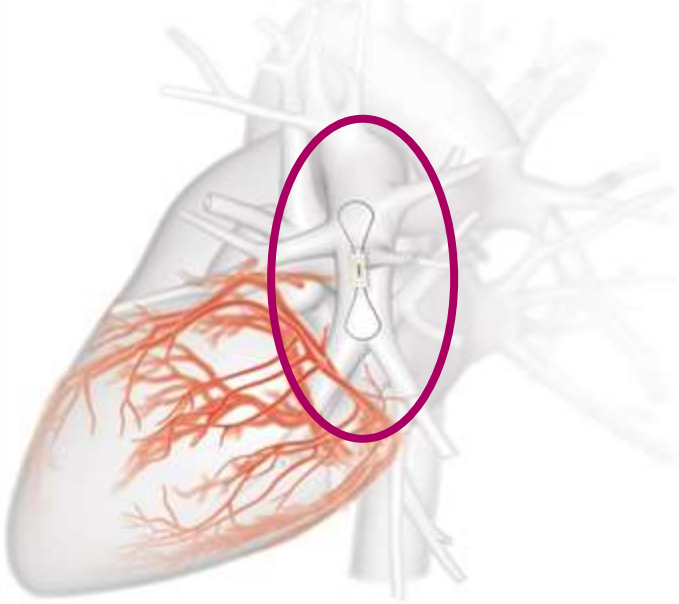
- **Delivers insight into the early onset of worsening HF to more proactively manage HF patients and improve outcomes**

PULMONARY ARTERY PRESSURE SENSOR

PATIENT ELECTRONICS SYSTEM

MERLIN.NET™ PCN

TARGET LOCATION FOR PA PRESSURE SENSOR

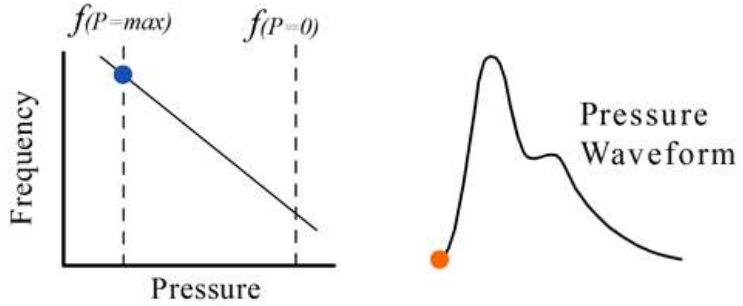


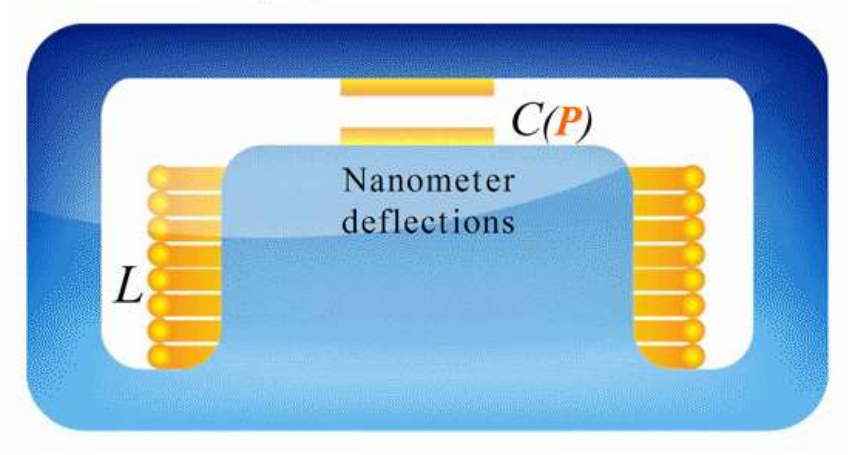
- Abraham WT, *Lancet*, 2011.

Microelectrical Mechanical System (MEMS)

No lead or battery, no need for replacement

$$f = \frac{1}{2\pi\sqrt{L\ C(P)}}$$



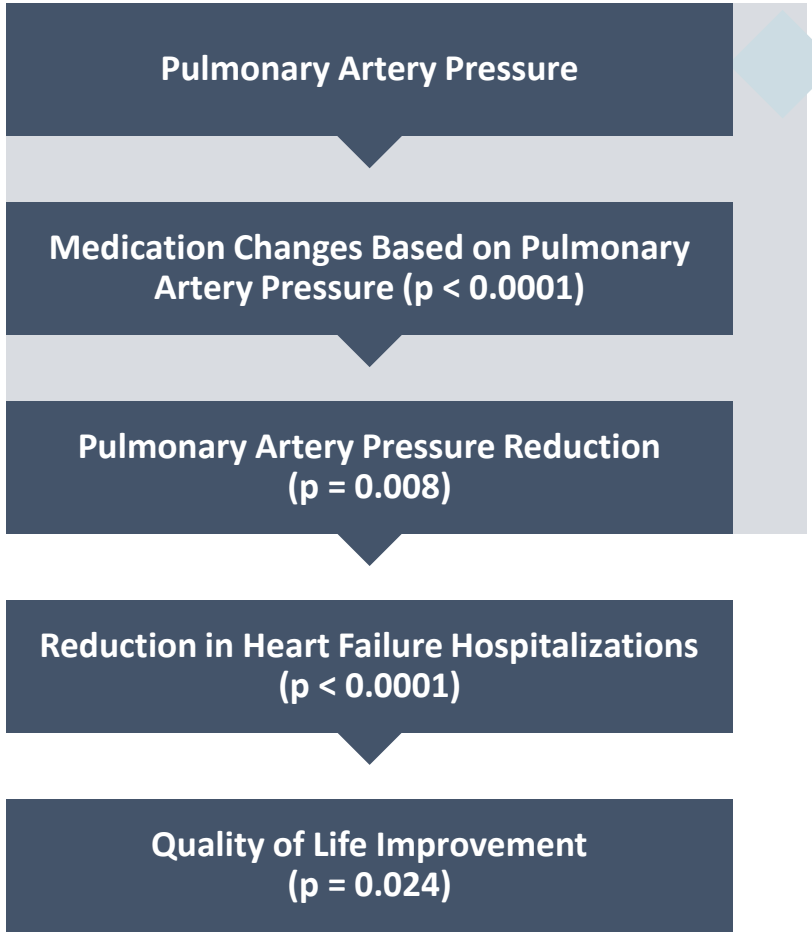


The CardioMEMS™ HF System Implant Procedure

- **PA PRESSURE SENSOR IS INSERTED DURING A RIGHT HEART CATHETERIZATION PROCEDURE VIA FEMORAL VEIN APPROACH.**

Summary of CHAMPION Randomized Clinical Trial:

550 PREVIOUSLY HOSPITALIZED NYHA CLASS III PATIENTS



MANAGING PRESSURES TO TARGET GOAL RANGES:

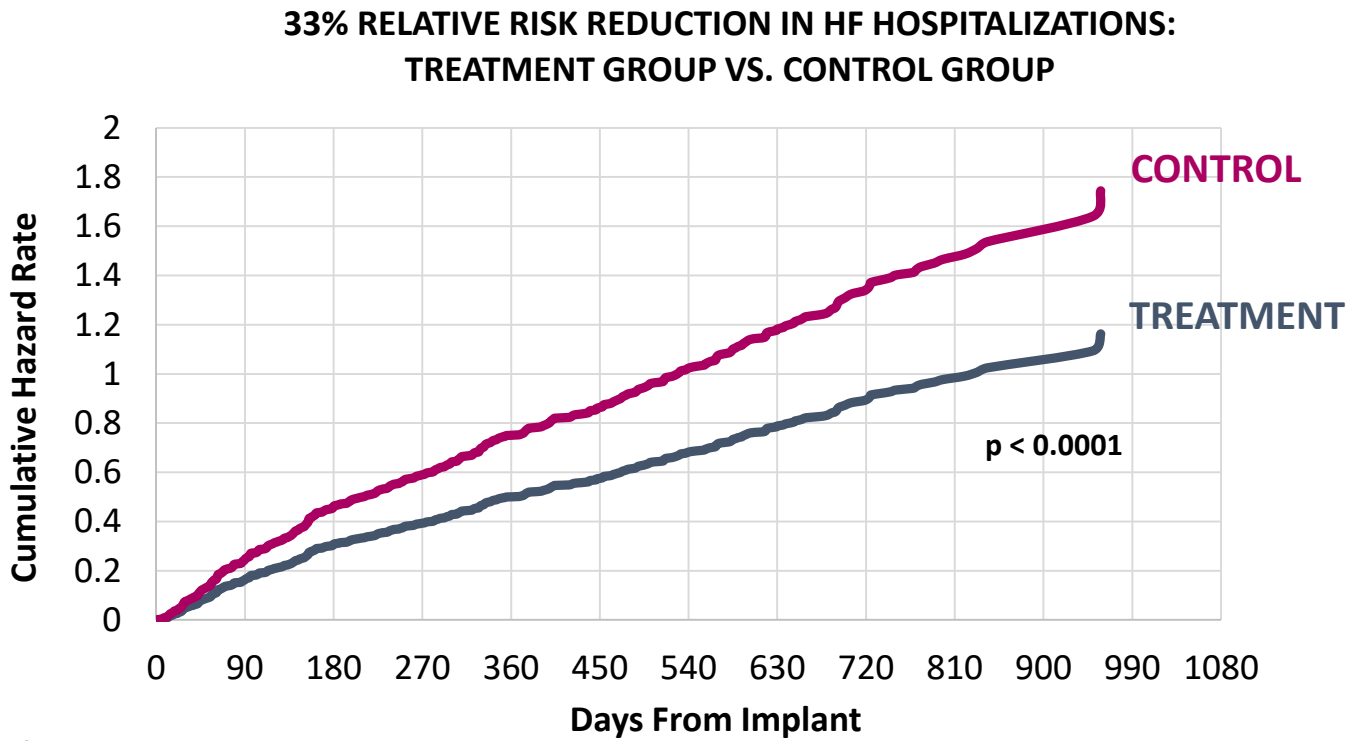
- PA pressure systolic 15–35 mmHg
- PA pressure diastolic 8–20 mmHg
- PA pressure mean 10–25 mmHg

Using diuretics and vasodilators, in addition to guideline-directed medical therapies

1. Abraham WT, et al. *Lancet*, 2011.
2. Abraham WT, et al. *Lancet*, 2016.
3. Adamson PB, et al. *J Card Fail*, 2010.

Primary Efficacy Endpoint Met with Significantly Reduced Heart Failure Hospitalization

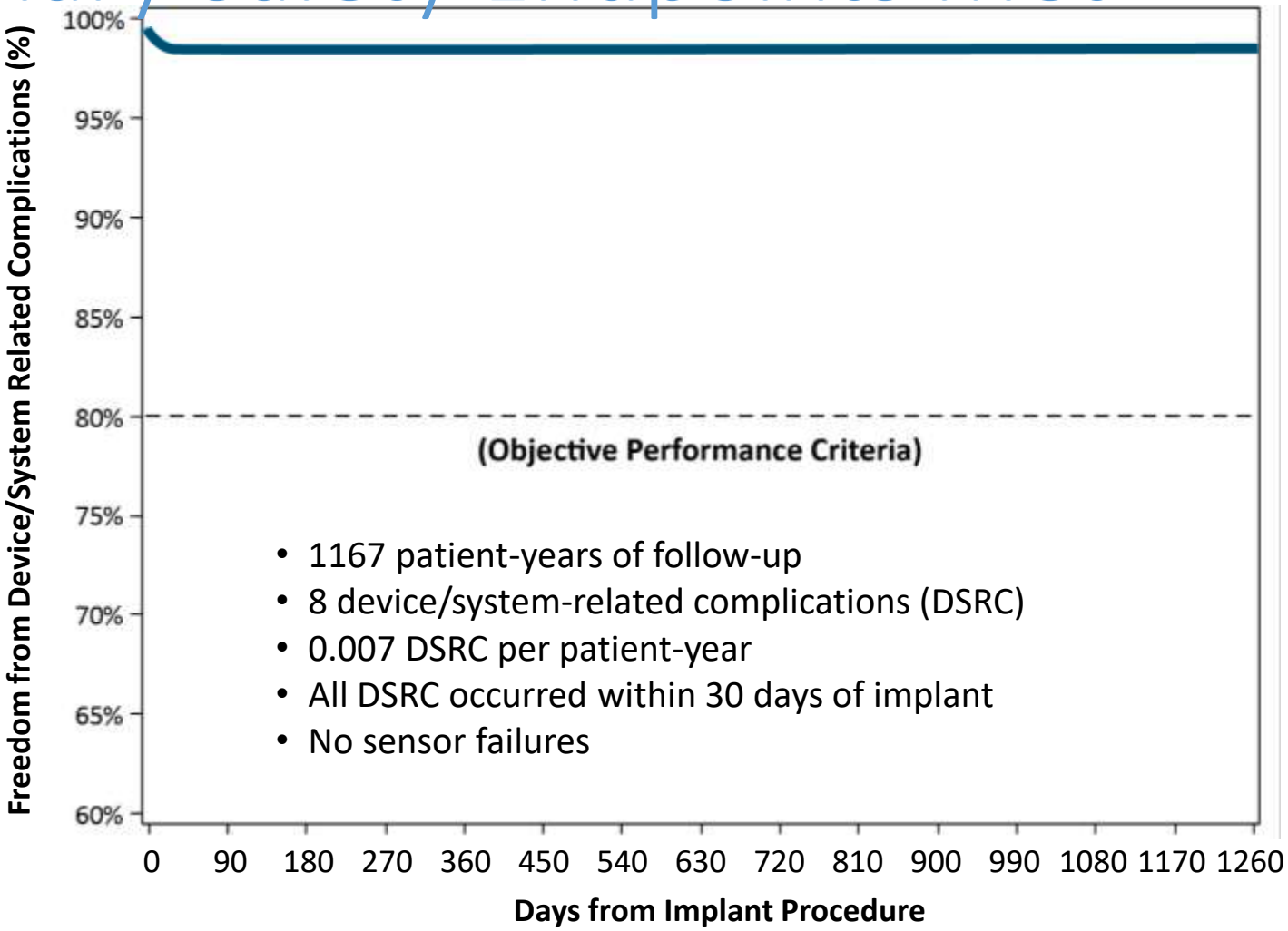
- **PART 1: RANDOMIZED ACCESS**



No. at Risk													
CONTROL	280	267	254	241	210	175	131	101	62	27	12	5	0
TREATMENT	270	262	246	235	197	164	125	105	75	38	8	3	0

- Abraham W, et al. *Lancet*, 2016.

Both Primary Safety Endpoints Met



All Secondary Endpoints Met

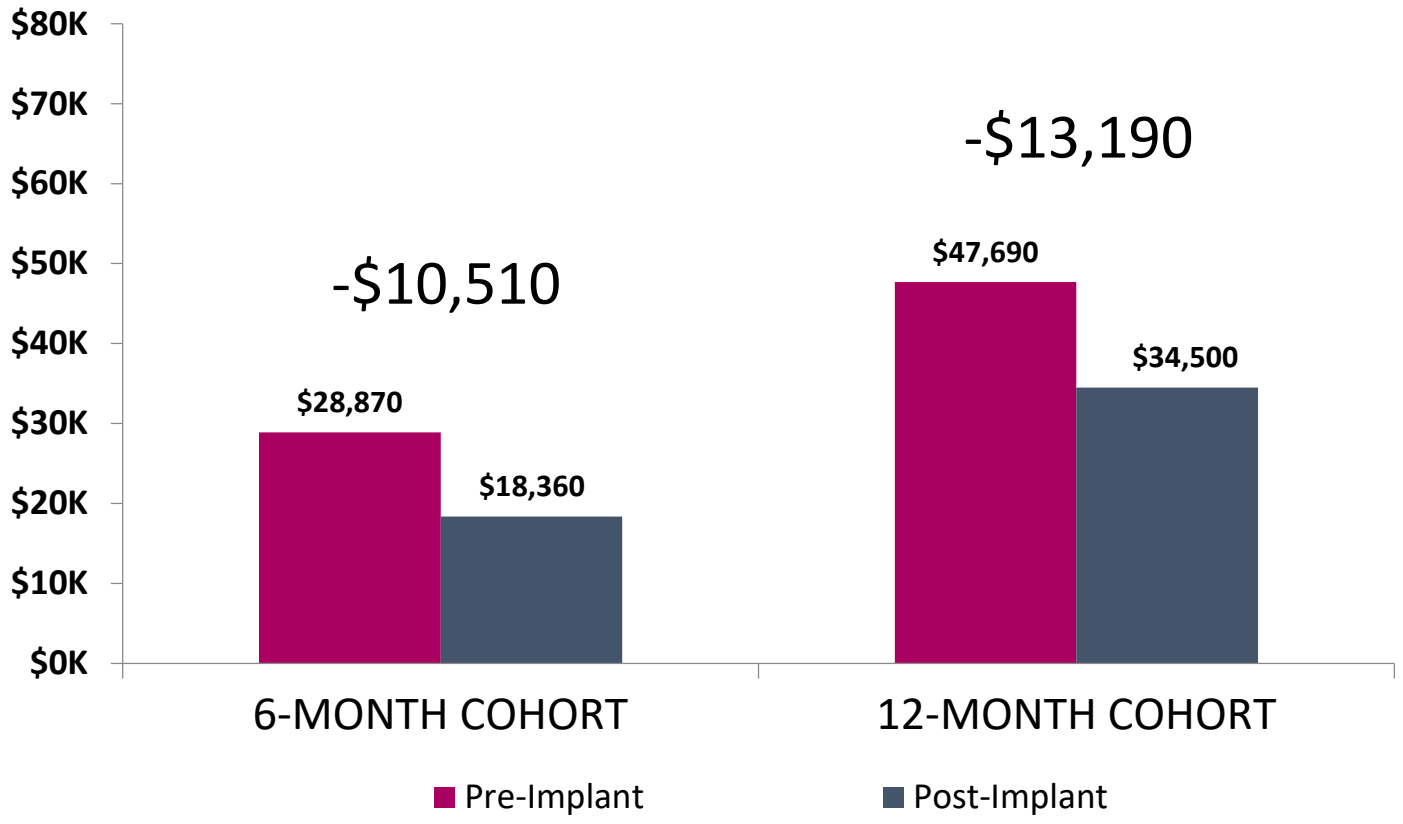
PART 1: RANDOMIZED ACCESS

		TREATMENT (N = 270)	CONTROL (N = 280)	P-VALUE
SECONDARY ENDPOINTS	Change from baseline in PA mean pressure (mean AUC [mmHg x days])	-156	33	0.008
	Number and proportion of patients hospitalized for HF (%)	55 (20%)	80 (29%)	0.03
	Days alive and out of hospital for HF (mean ± SD)	174.4 ± 31.1	172.1 ± 37.8	0.02
	Quality of life (Minnesota Living with Heart Failure Questionnaire, mean ± SD)	45 ± 26	51 ± 25	0.02

- *Total of 8 DSRCs including 2 events in Consented not implanted patients (n = 25)
- Abraham WT, et al. *Lancet*, 2011.

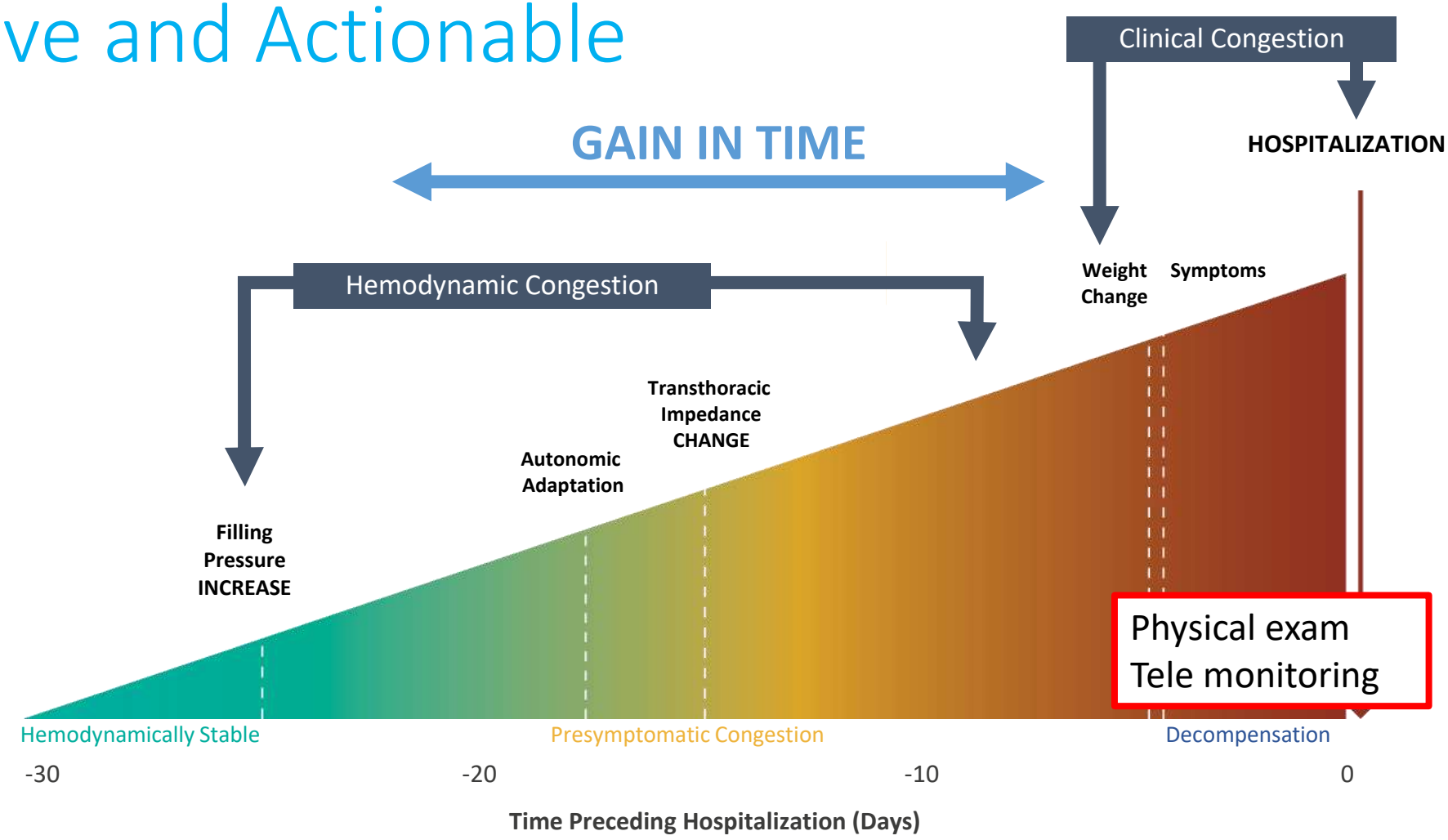
Real-world Use of the CardioMEMS™ HF System:

ASSOCIATED HF HOSPITALIZATION COSTS



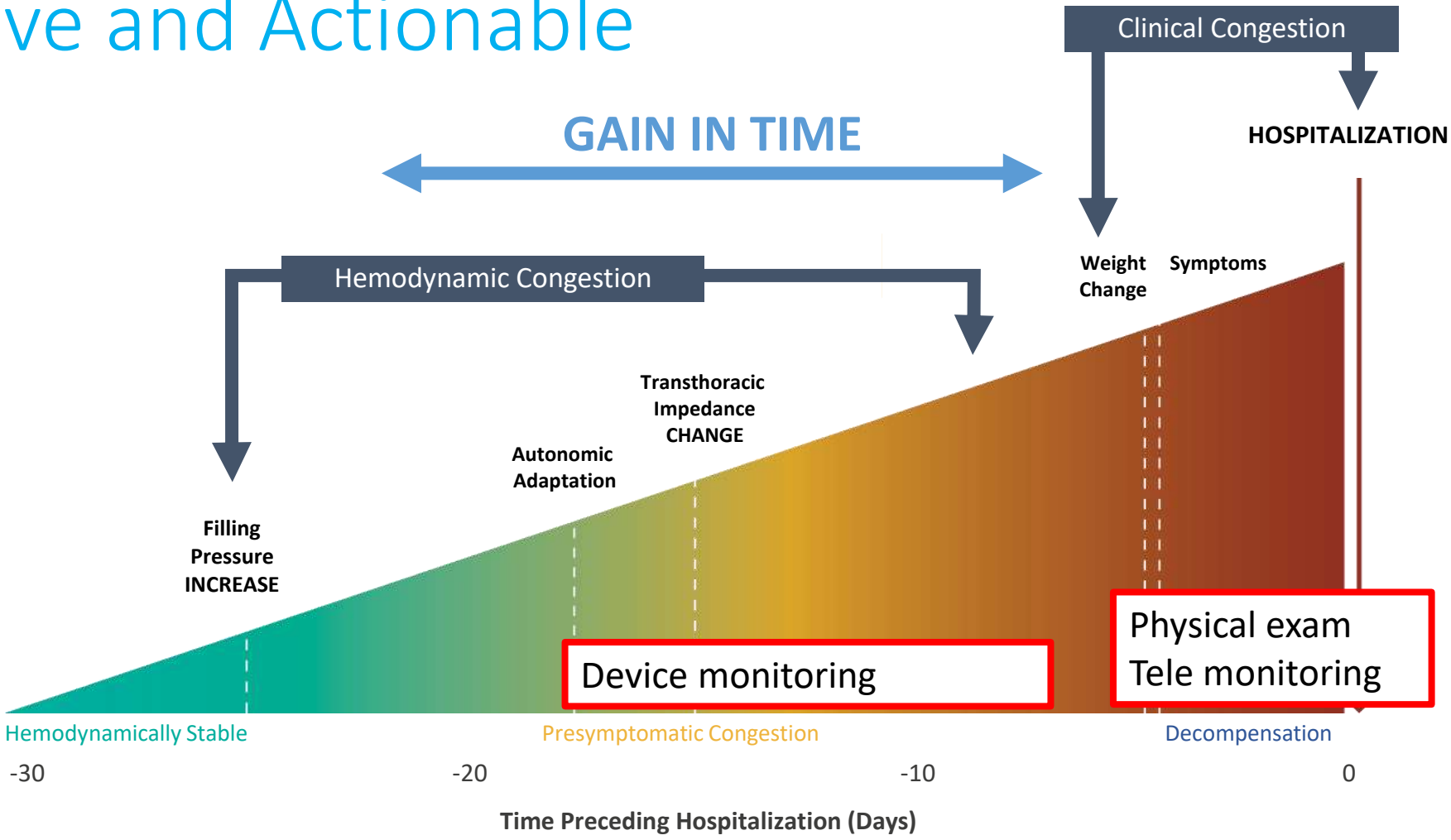
Large (N = 1114) retrospective cohort study using the CardioMEMS™ HF System patients from CMS database
Desai, AS, et al. *J Am Coll Cardiol*, 2017;69(19):2357–65.

Monitoring Pulmonary Artery Pressures, Proactive and Actionable



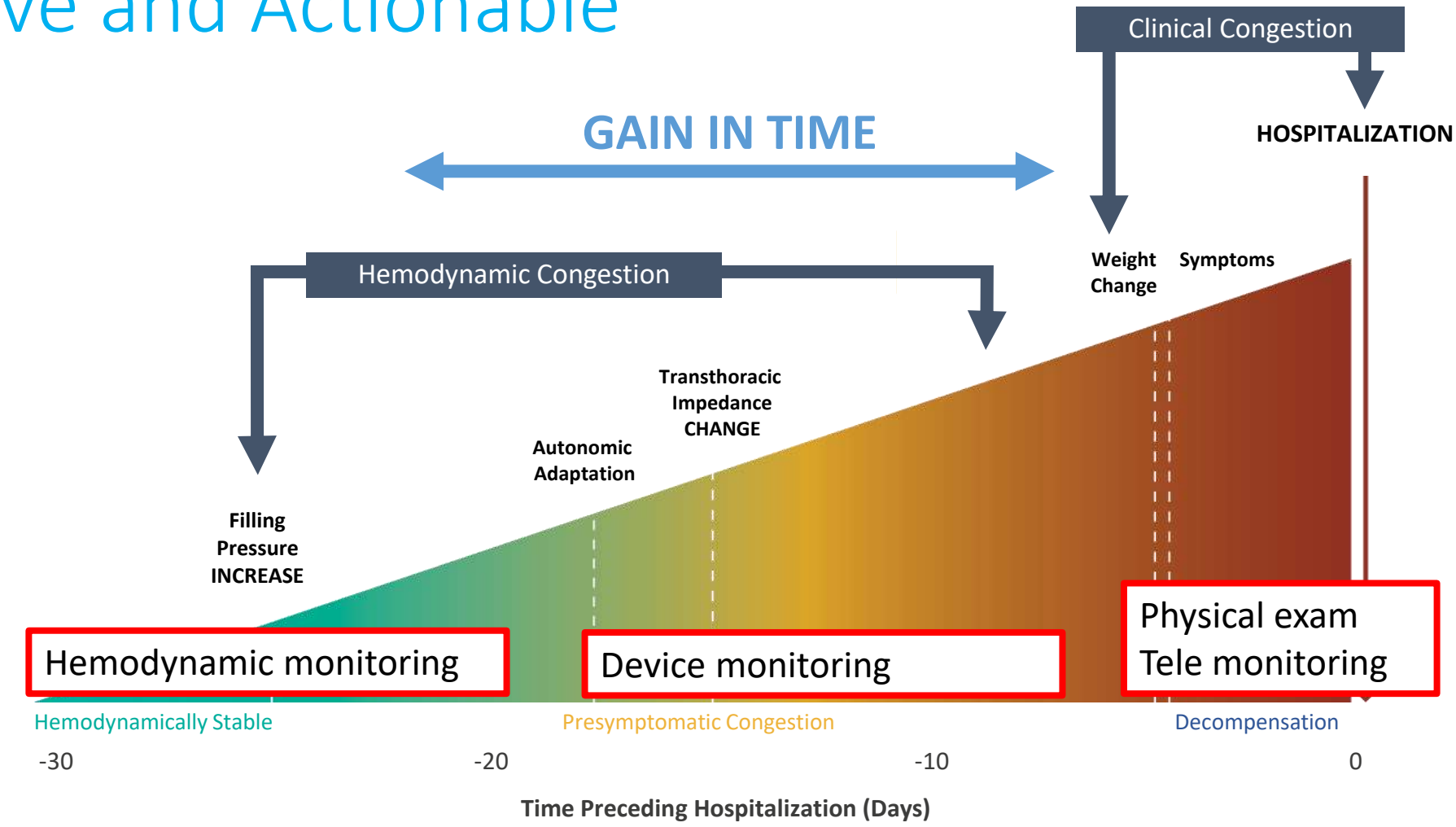
- Adamson PB, et al. *Curr Heart Fail Reports*, 2009.

Monitoring Pulmonary Artery Pressures, Proactive and Actionable



- Adamson PB, et al. *Curr Heart Fail Reports*, 2009.

Monitoring Pulmonary Artery Pressures, Proactive and Actionable



- Adamson PB, et al. *Curr Heart Fail Reports*, 2009.

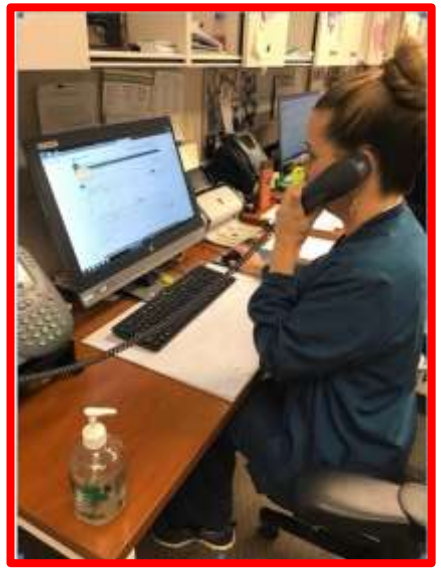
Information Overload

MA/Nurse

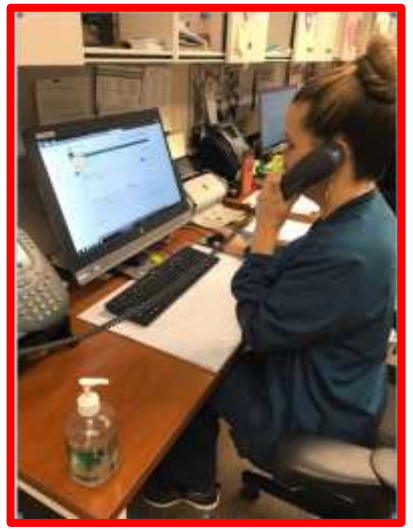
APP/Physician

Workflow

Patient transmits daily



MA/Nurse reviews twice weekly initially and then prn for alerts



HF NP Reviews and adjusts treatment plan

HF physician

EP njurse reviews and adjusts treatment

EP Physician

Virtual HF clinic-Key elements

- **Identify key team members**
- **Patient selection**
- **Policies and procedures for monitoring**
- **Establish workflows/Orders**
- **Staffing**
- **Alerts**
- **Keep medication changes on website**
- **Education**
  - Providers
  - Patients
  - Staff

Buy in from other providers
Network support for resources and staffing

The End

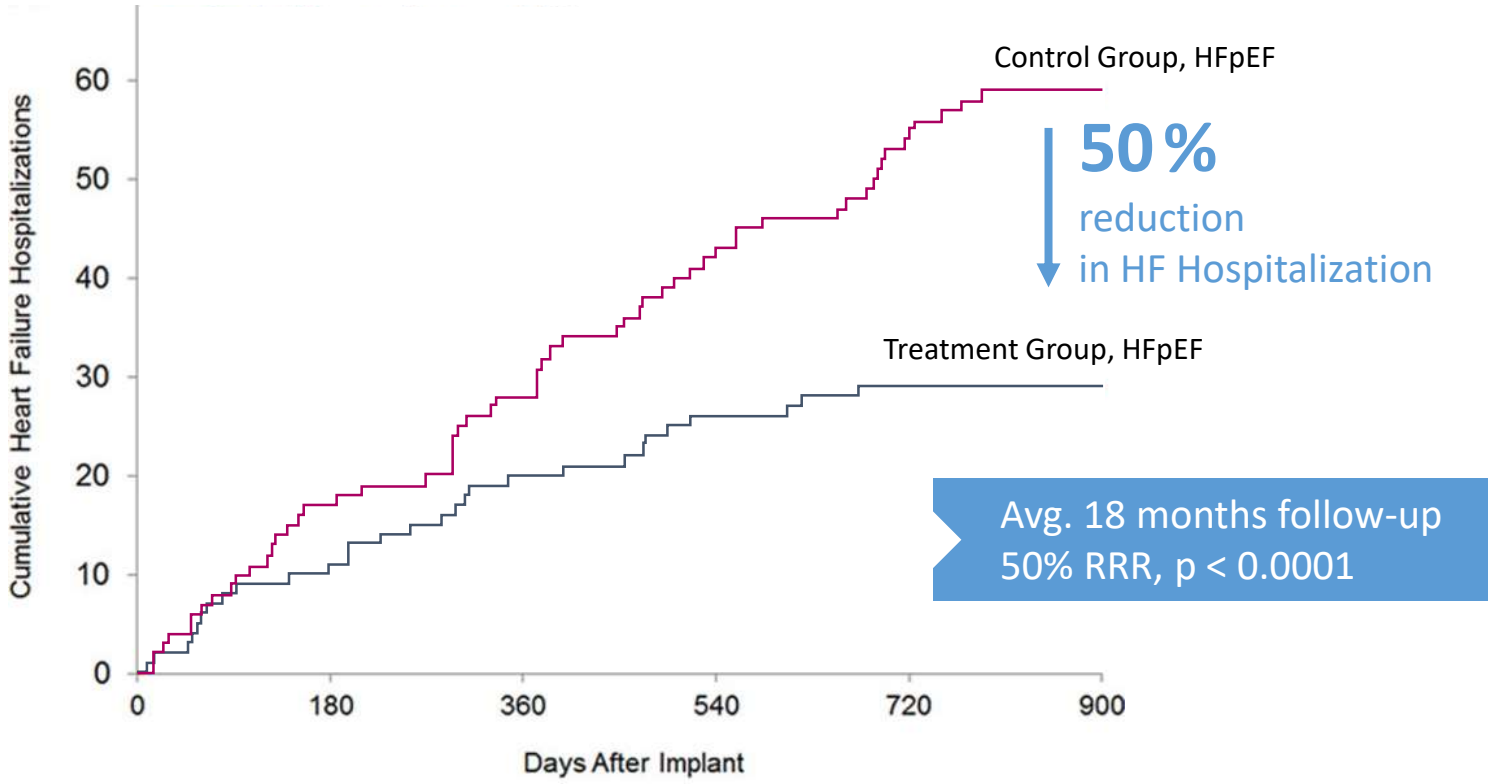
The CHAMPION Trial Subgroup Analyses

PROSPECTIVE ANALYSES:

- Effects of PAP pressure monitoring on:

Prospective Subgroup Analysis:

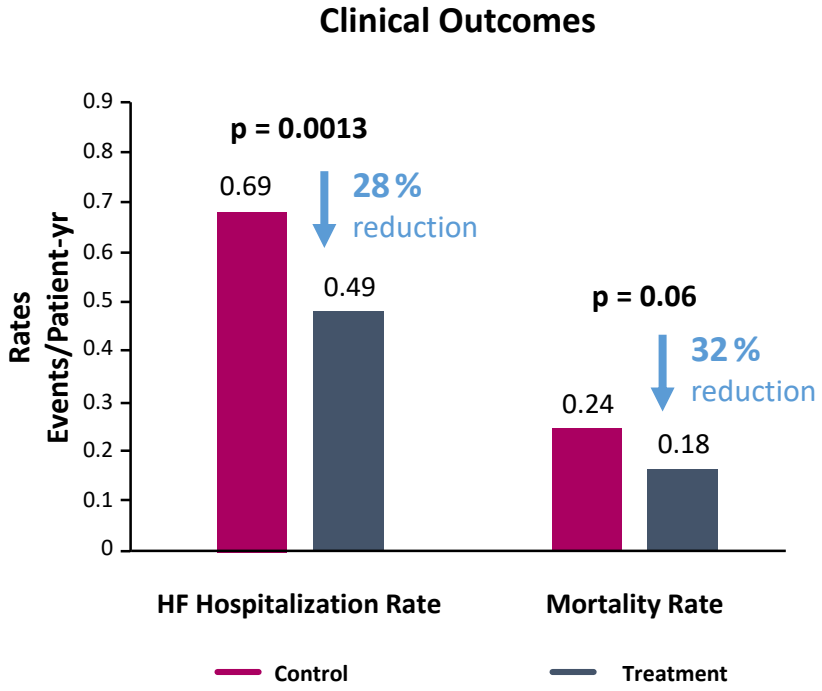
HFpEF PATIENTS MANAGED WITH THE CardioMEMS™ HF SYSTEM SHOW SIGNIFICANT REDUCTION IN HF Hospitalization

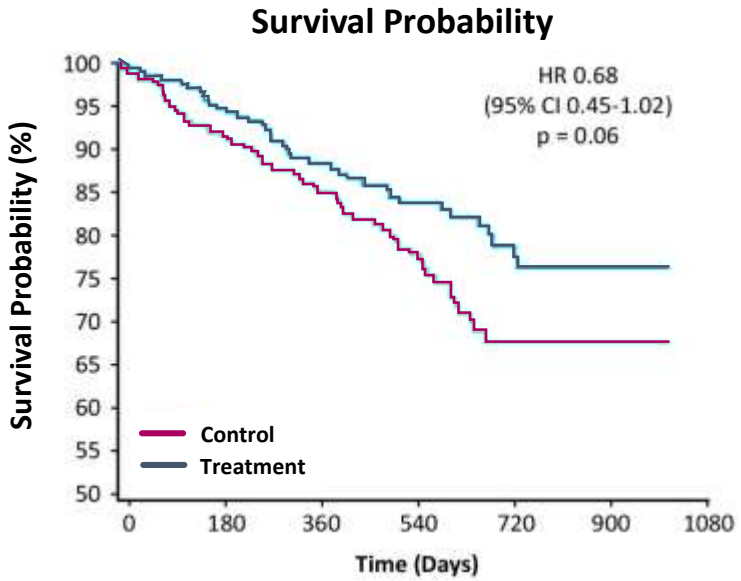


- Adamson PB, Abraham WT, Bourge RC, et al. *Circ Heart Fail*, 2014 Nov;7(6):935-44.

Prospective Subgroup Analysis:

HFrEF PATIENTS SHOWS SIGNIFICANT REDUCTION IN HF Hospitalization AND STRONG TREND TOWARDS IMPROVED SURVIVAL*





No. at Risk

CONTROL	234	209	173	102	45	7	0
TREATMENT	222	202	161	105	62	7	0

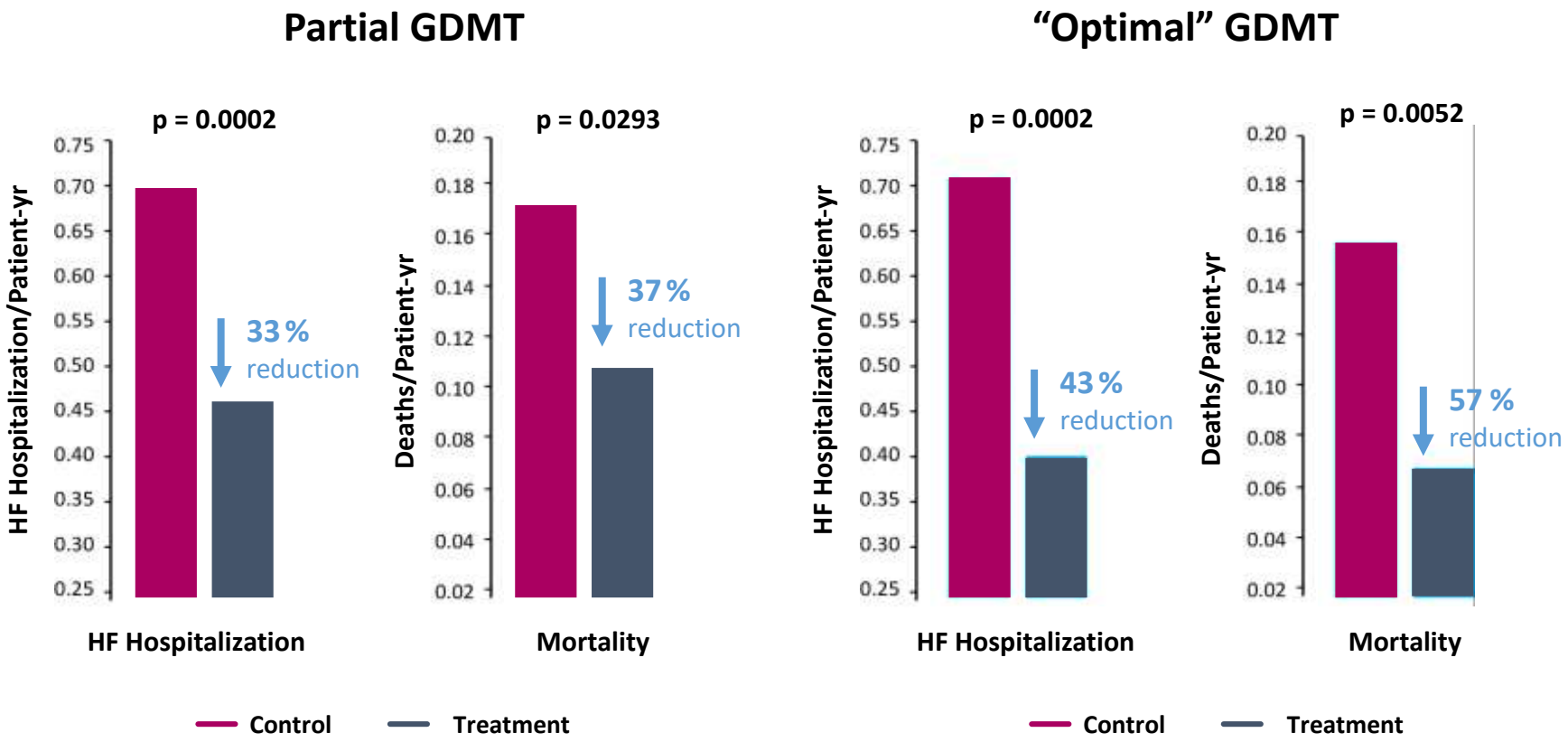
Kaplan-Meier Survival Analysis

*The CardioMEMS™ HF System is not labeled for a reduction in mortality

Givertz M, et al. *J Am Coll Cardiol*, 2017.

Retrospective Subgroup Analysis:

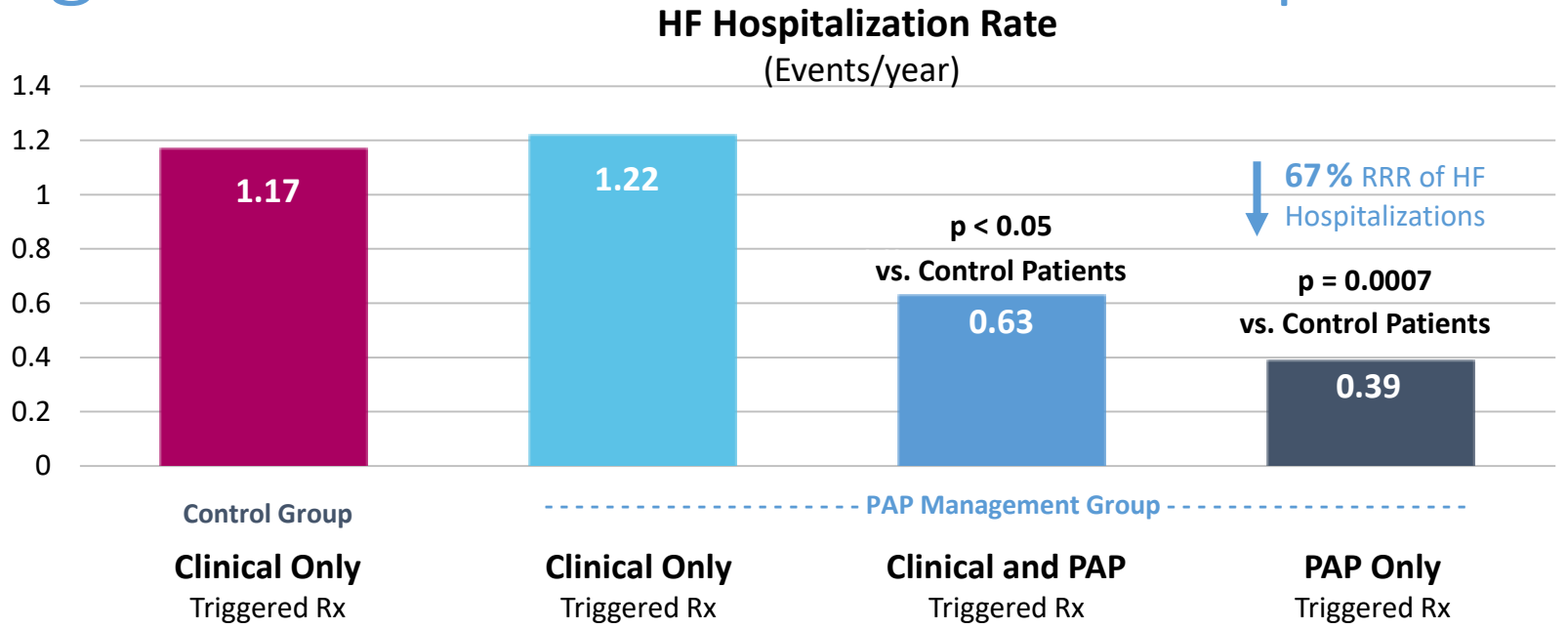
HFrEF PATIENTS SHOW SYNERGY BETWEEN OPTIMAL GDMT AND HEMODYNAMIC CARE



*The CardioMEMS™ HF System is not labeled for a reduction in mortality

Givertz M, et al. *J Am Coll Cardiol,* 2017.

Managing GDMT Based on PA Pressures Alone Led to Significant Reduction in HF Hospitalization

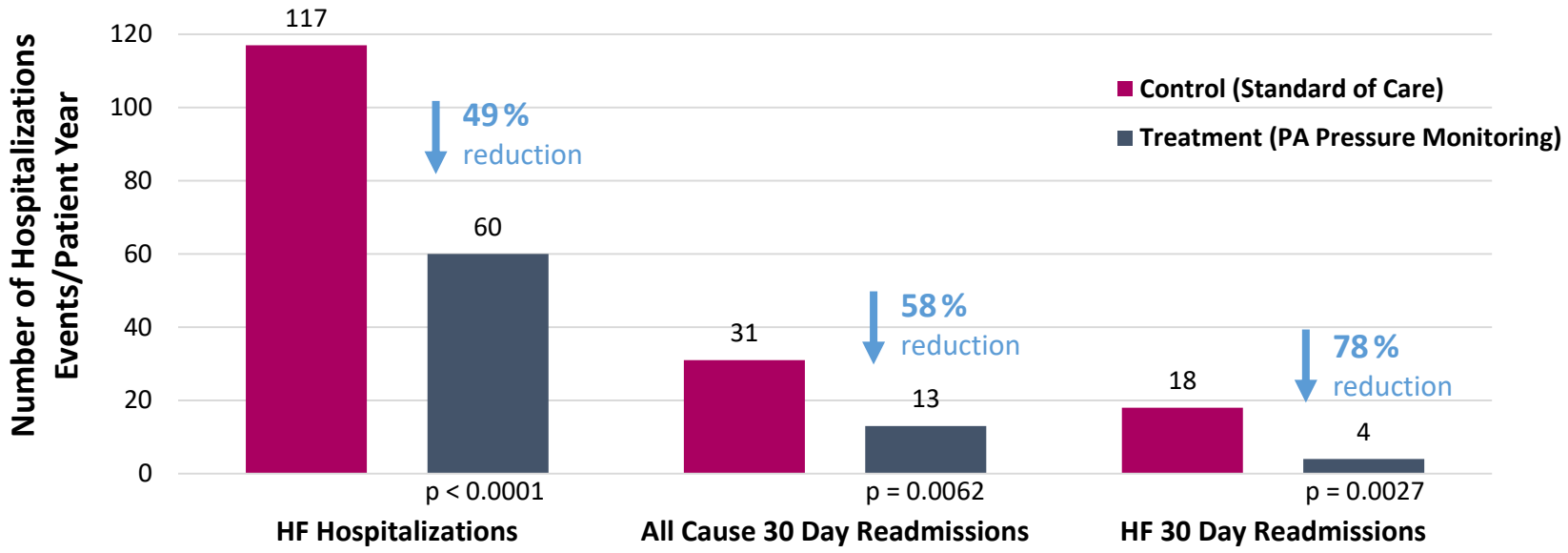


Managing medical therapy based on PA pressures, along with follow-up lab and patient assessment led to **SIGNIFICANTLY BETTER OUTCOMES THAN MANAGING BASED ON CLINICAL SIGNS AND SYMPTOMS**

Goldberg, et al. *HRS* 2015.

Subgroup Analysis:

MEDICARE-ELIGIBLE POPULATION SHOWS SIGNIFICANT REDUCTION IN 30-DAY READMISSIONS

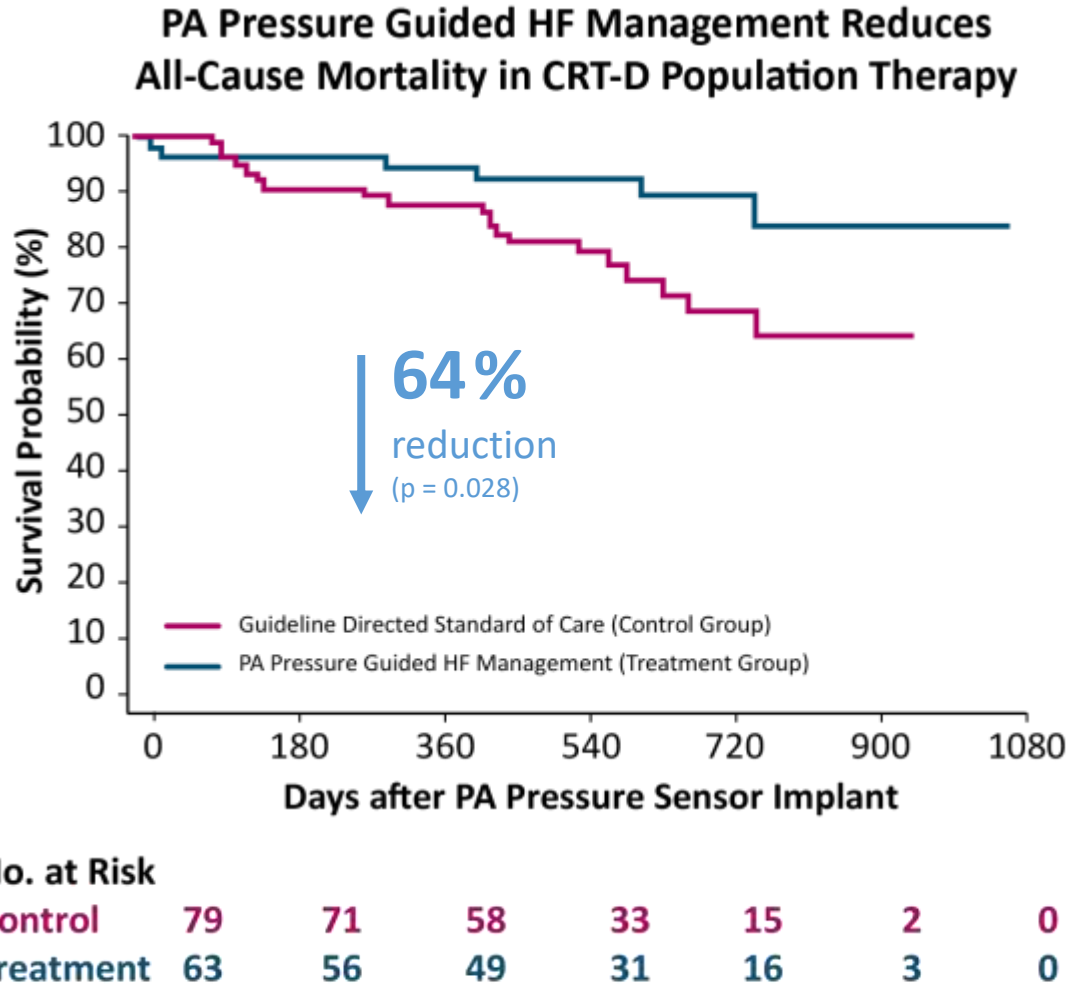


STATISTICALLY SIGNIFICANT REDUCTIONS in 30-day readmission and HF Hospitalization in Medicare-eligible patients 65 years or older (n = 245), when PA pressures are monitored using the CardioMEMS™ HF System.

Adamson, et al. *Circ Heart Fail*, 2016.

Subgroup Analysis:

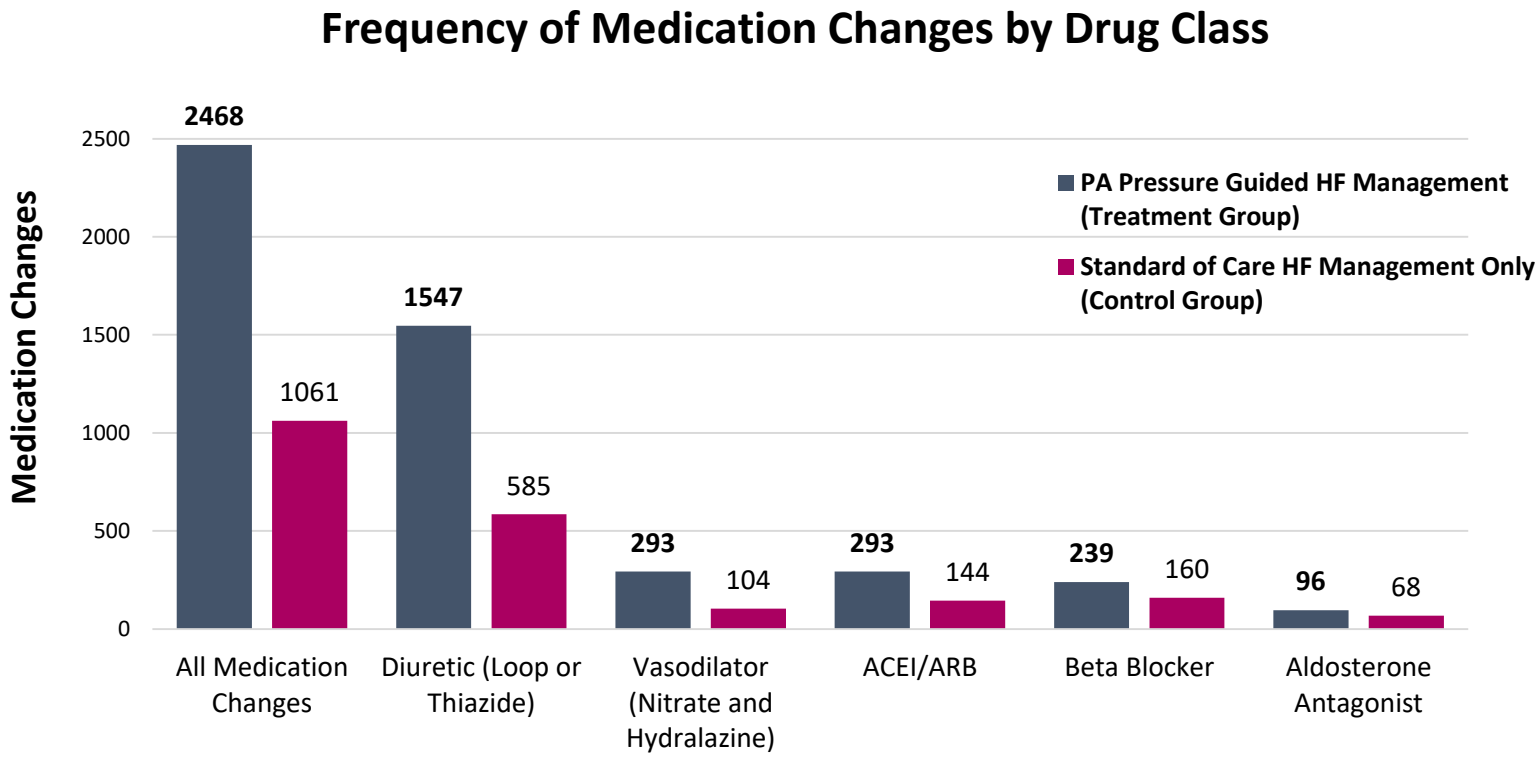
HFrEF PATIENTS WITH CRT-D FOLLOWING GDMT



Abraham, et al. *HRS* 2015.

Subgroup Analysis:

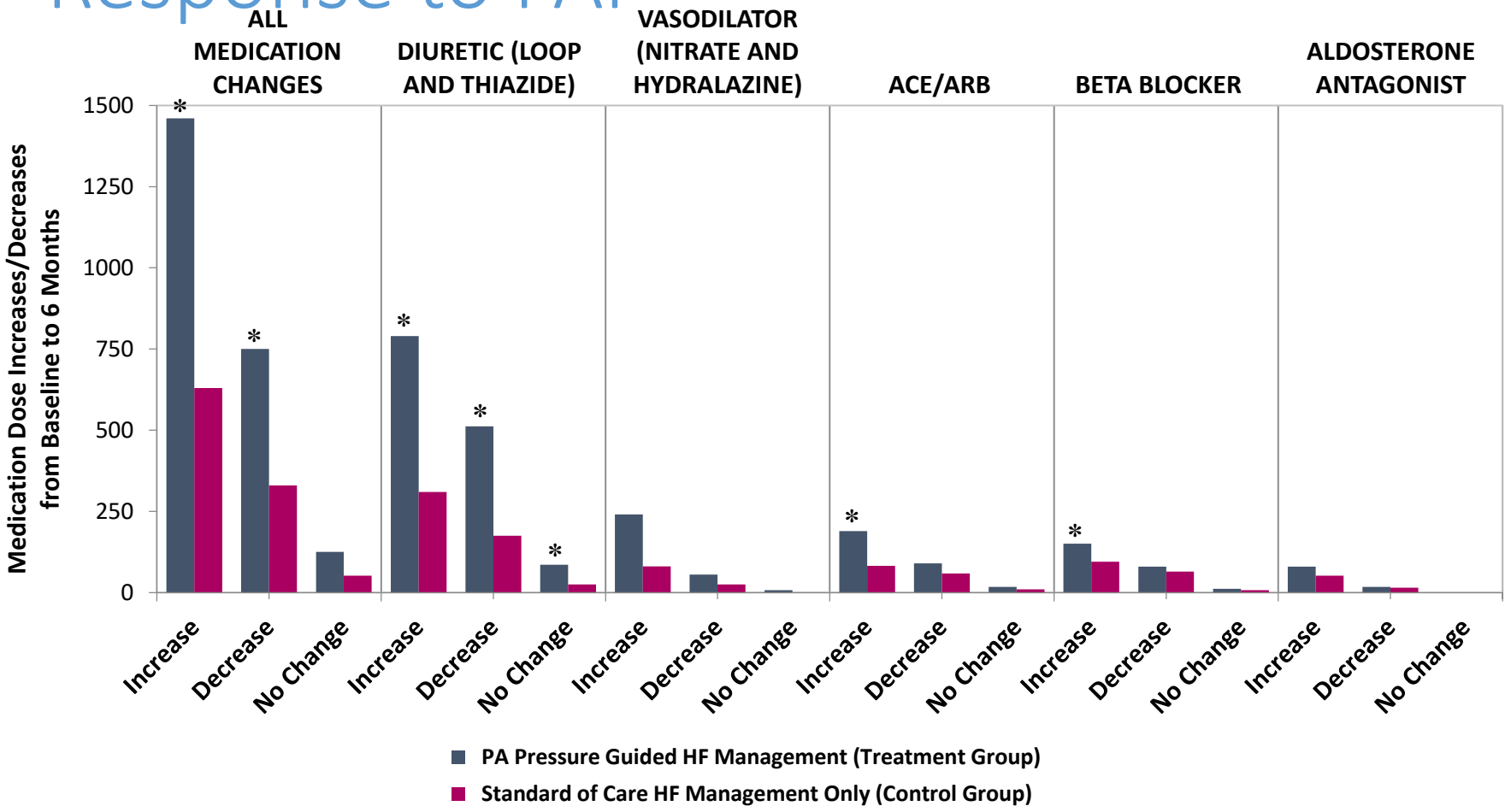
PA-GUIDED MEDICAL MANAGEMENT



Medication changes based on PA pressure information were **MORE EFFECTIVE IN REDUCING HF HOSPITALIZATIONS** than using signs and symptoms alone.

Costanzo, et al. *J Am Coll Cardiol Heart Failure,* 2016.

Medication Increases and Decreases in Response to PAP



*p < 0.05 PA Pressure Guided HF Management vs. Standard of Care HF Management

No Change represents where a medication was changed (ie., dose frequency, route, etc.) which resulted in no net dose equivalent change

Costanzo MR, et al. *J Am Coll Cardiol HF,* 2016.

The CHAMPION Trial Subgroup Analyses:

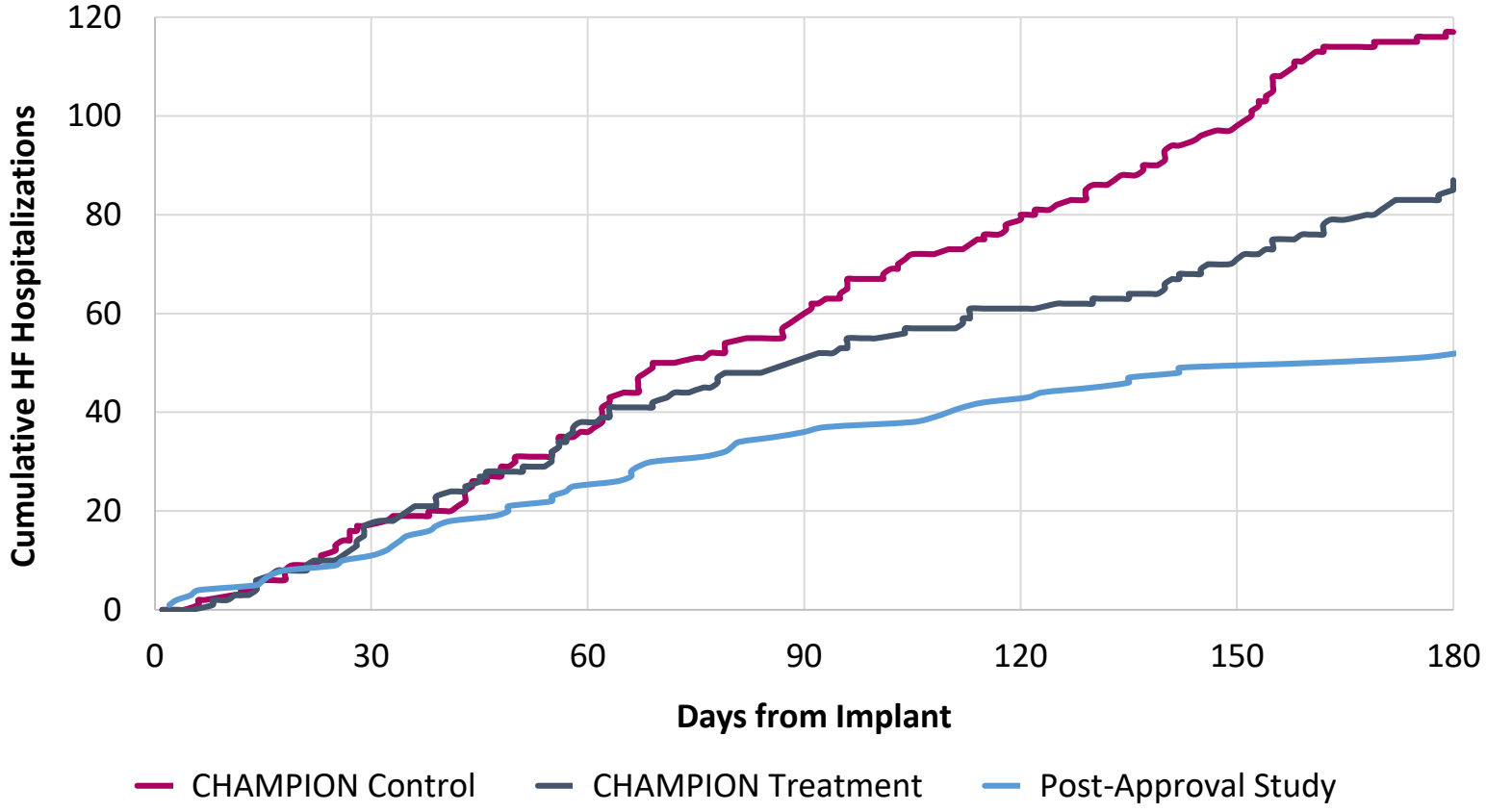
REDUCTION OF HF HOSPITALIZATION IN PATIENT GROUPS WITH COMMON COMORBIDITIES

Sub-Group or Comorbidity	n (control)	n (treatment)	Follow-up Period (months)	Reduction of HF Hospitalization Rate in Treatment Group vs. control
Medicare population[1]	125	120	18	49%, $p < 0.0001$
HFpEF[2]	56	59	18	50%, $p < 0.0001$
HFrEF following GDMT[3]	174	163	17	43%, $p < 0.0001$
CRT-D or ICD following GDMT[4]	146	129	18	43%, $p < 0.0001$
History of myocardial infarction[5]	137	134	15	46%, $p < 0.001$
COPD[6,7]	96	91	15	41%, $p = 0.0009$
Pulmonary hypertension[8]	163	151	15	36%, $p = 0.0002$
AF[9]	135	120	15	41%, $p < 0.0001$
Chronic kidney disease[10]	150	147	15	42%, $p = 0.0001$

Patients with common HF comorbidities and patients in important subgroups **HAVE CONSISTENT REDUCTION IN HF HOSPITALIZATIONS** with PA pressure-guided therapy.

1. Adamson, et al. *Circ Heart Fail*, 2016.
2. Adamson, et al. *Circ Heart Fail*, 2014.
3. Abraham, et al. *ACC*, 2015.
4. Abraham, et al. *HRS* 2015.
5. Strickland WL, et al. *J Am Coll Cardiol*, 2011.
6. Criner G, et al. *Eur Respir J*, 2012.
7. Martinez F, et al. *Eur Respir J*, 2012.
8. Benza R, et al. *J Card Fail*, 2012.
9. Miller AB, et al. *J Am Coll Cardiol*, 2012.
10. Abraham, et al. *J Card Fail*, 2014.

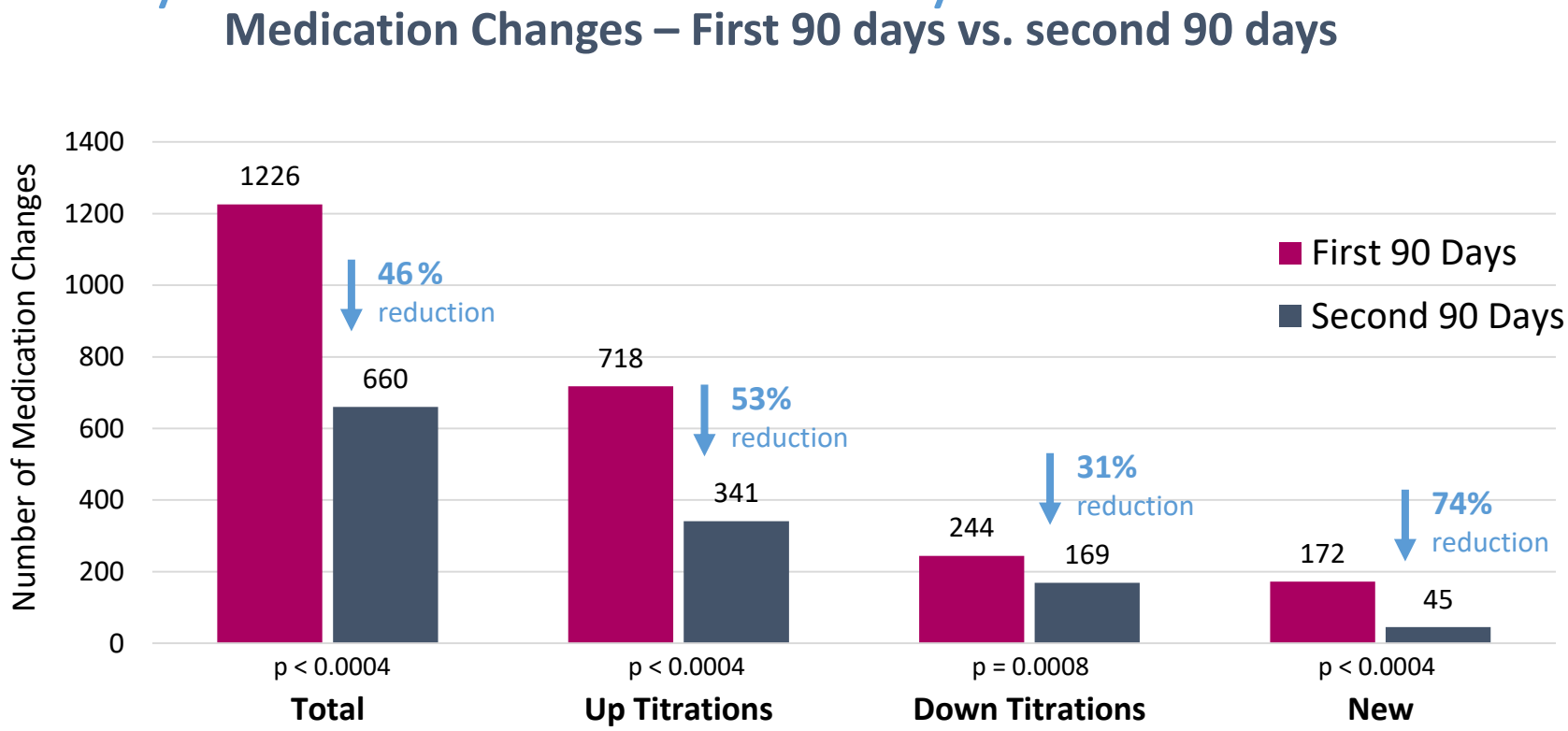
Reduction of HF Hospitalization in the CardioMEMS™ HF System Post-Approval Study



In the post-approval study, there were 56 HF Hospitalizations (0.20 events/pt-6m) in 43 pts

Raval, et al. Presented at HFSA 2017.

Medication Changes Significantly Reduced in First 90 Days vs. Second 90 Days in the PAS

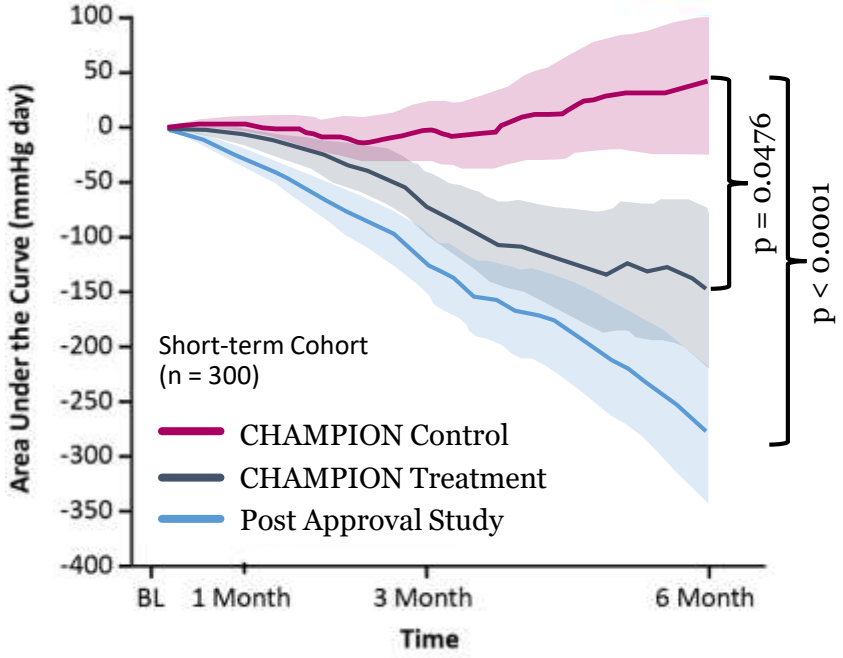


65% of the overall HF medication changes were made in the first 90 days, with trends of stabilization and significantly fewer medication changes during the second 90 days.

Raval, et al. Presented at HFSA 2017.

The CardioMEMS™ HF System PAS Short-term Results

REDUCED HF Hospitalization AND MEAN PAP



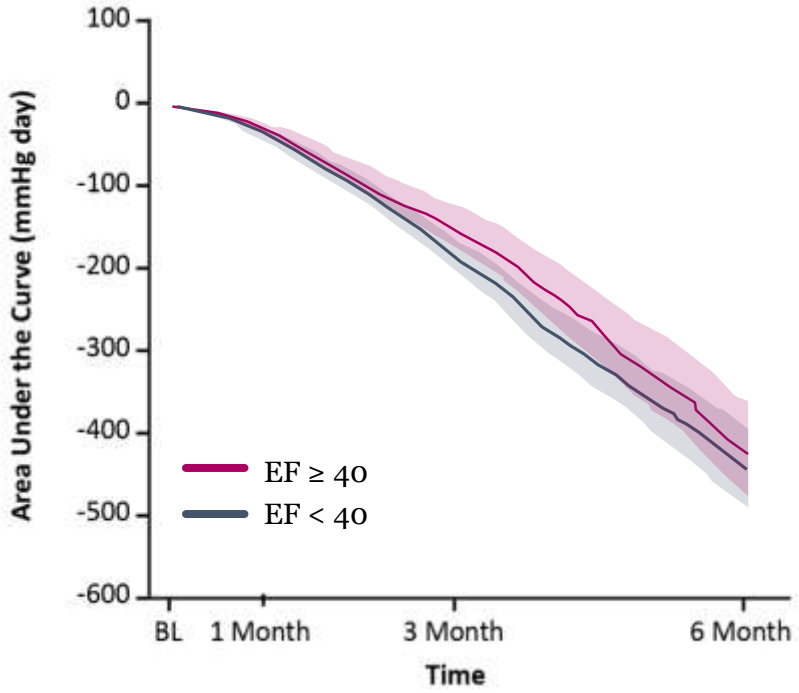
AUC (mmHg day)			
	1 Month	**3 Months**	**6 Months**
CHAMPION Control (275 pts)	3.1 ± 6.7 (270 pts)	-5.5 ± 24.7 (251 pts)	42.0 ± 65.0 (228 pts)
CHAMPION Treatment (270 pts)	-7.0 ± 7.7 (266 pts)	-59.3 ± 27.6 (257 pts)	-150.1 ± 71.0 (236 pts)
PAS (300 pts)	-27.7 ± 7.0 (291 pts)	-112.6 ± 26.0 (275 pts)	-281.0 ± 63.5 (262 pts)

SIGNIFICANTLY GREATER REDUCTIONS IN MEAN PAP for the PAS cohort relative to the CHAMPION control group after 6 months, and **QUALITATIVELY GREATER REDUCTIONS** compared to the CHAMPION treatment group.

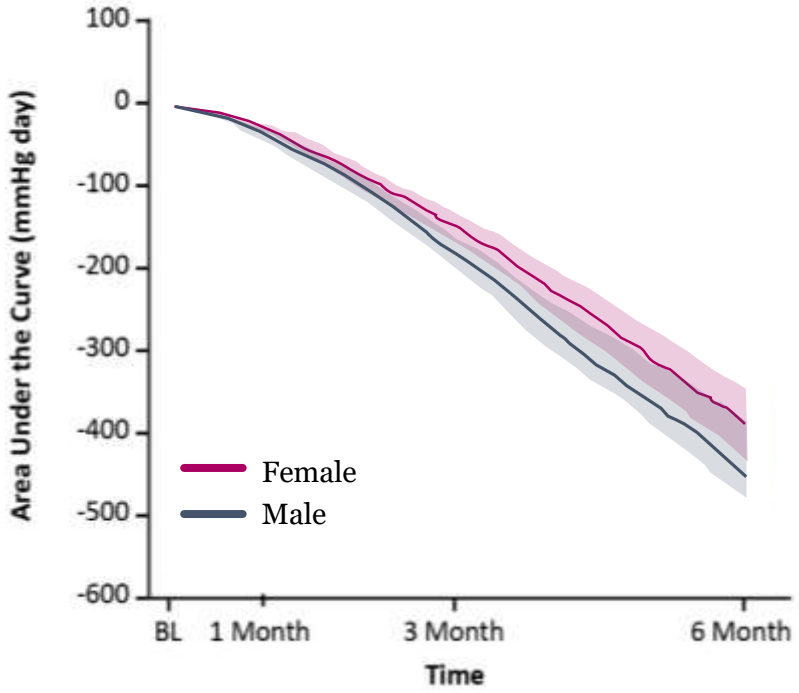
Raval, et al. Presented at HFSA 2017.

Pressures are Reduced Equally Well in HFrEF and HFpEF, as well as Male and Female

AUC Mean PAP Stratified by Ejection Fraction

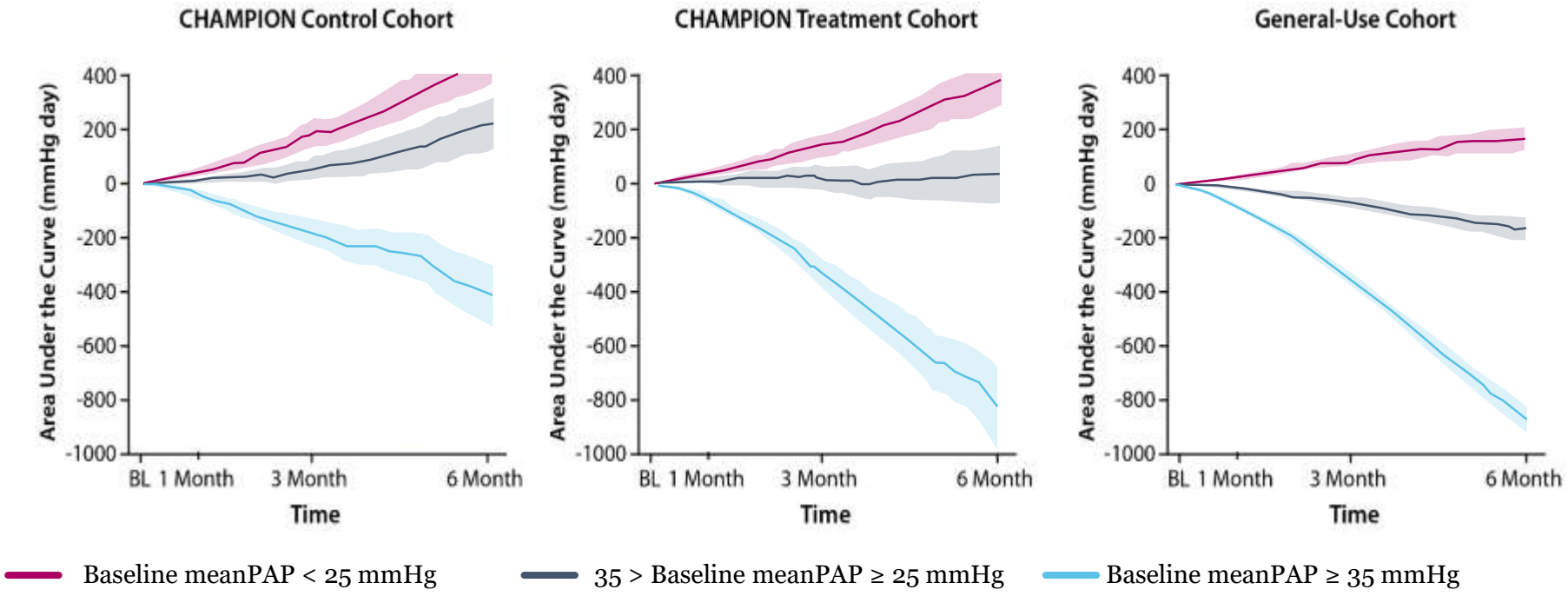


AUC Mean PAP Stratified by Gender



Heywood JT, Jermyn R, Shavelle D, et al. *Circulation* 2017;135: 1509–17.

Pressure Changes Stratified by Baseline PA Pressure



Greatest reduction in mean PAP observed for the CardioMEMS™ HF System patients with higher baseline PAP.

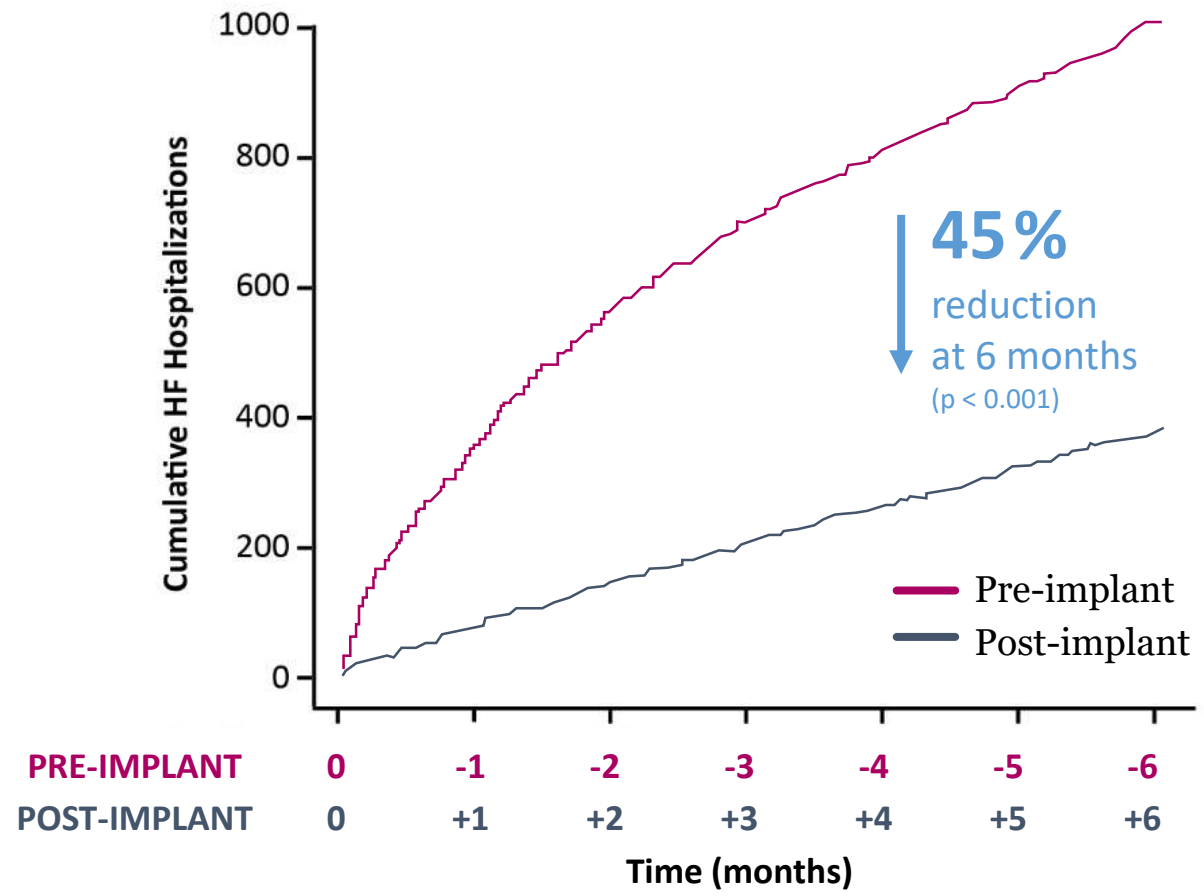
Patients in the treatment group with baseline PAP at goal, remained at goal over time.

Heywood JT, Jermyn R, Shavelle D, et al. *Circulation* 2017;135: 1509–17.

Real-world Use of the CardioMEMS™ HF System:

REDUCED HF HOSPITALIZATIONS

Cumulative HF Hospitalization During Period Before and After CardioMEMS™ HF System Implant

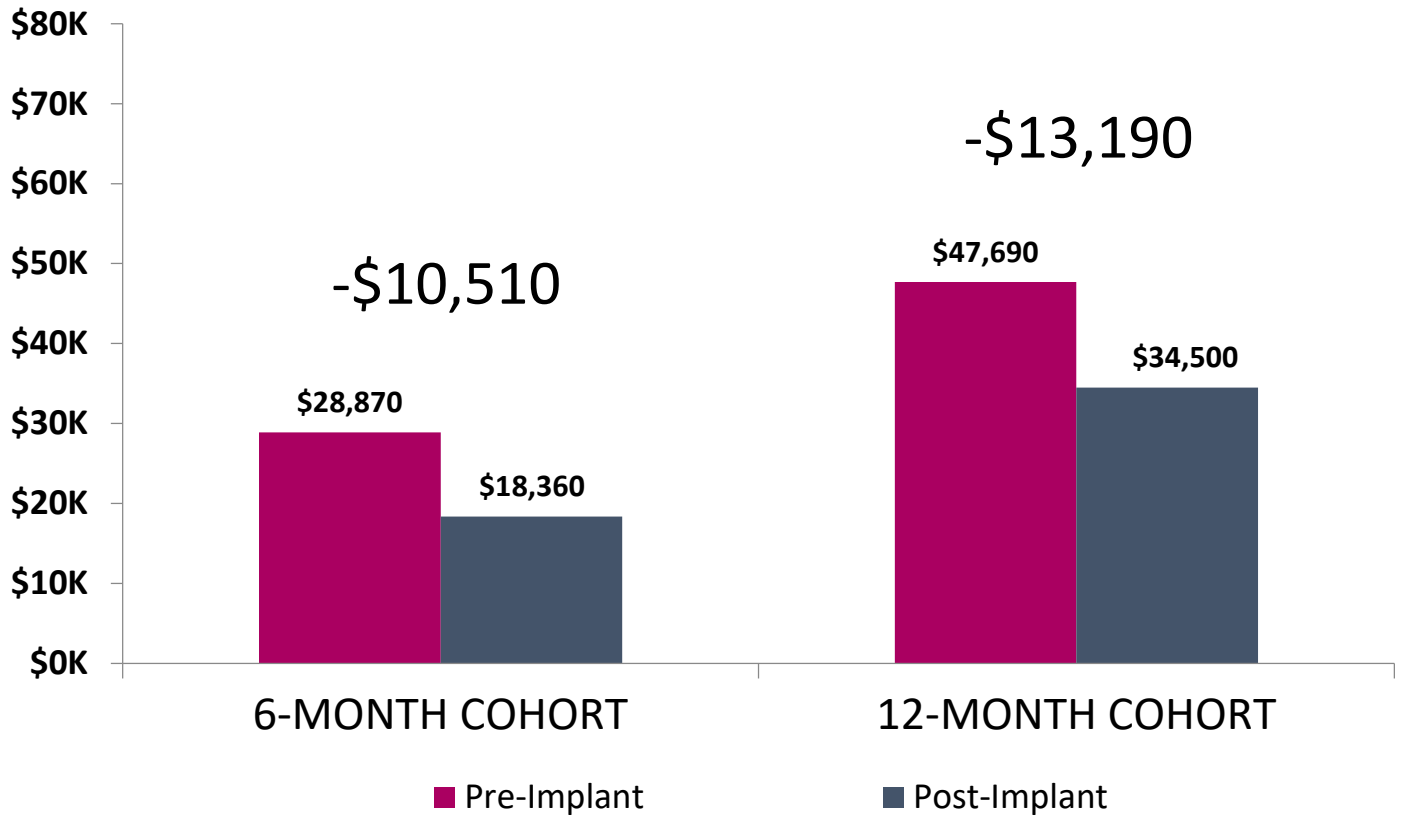


Large (N = 1114) retrospective cohort study using the CardioMEMS™ HF System patients from CMS database

Desai, AS, et al. *J Am Coll Cardiol*, 2017;69(19):2357–65.

Real-world Use of the CardioMEMS™ HF System:

ASSOCIATED HF HOSPITALIZATION COSTS

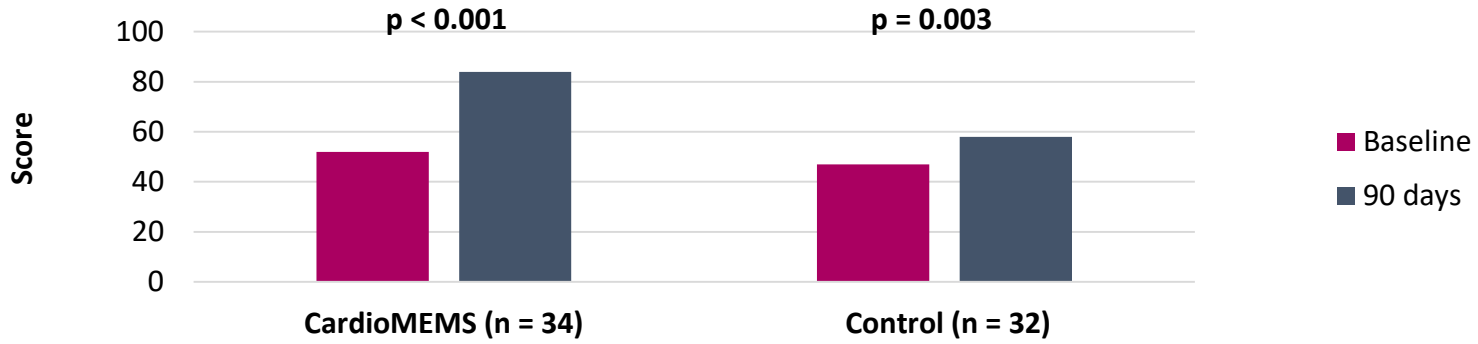


Large (N = 1114) retrospective cohort study using the CardioMEMS™ HF System patients from CMS database
Desai, AS, et al. *J Am Coll Cardiol*, 2017;69(19):2357–65.

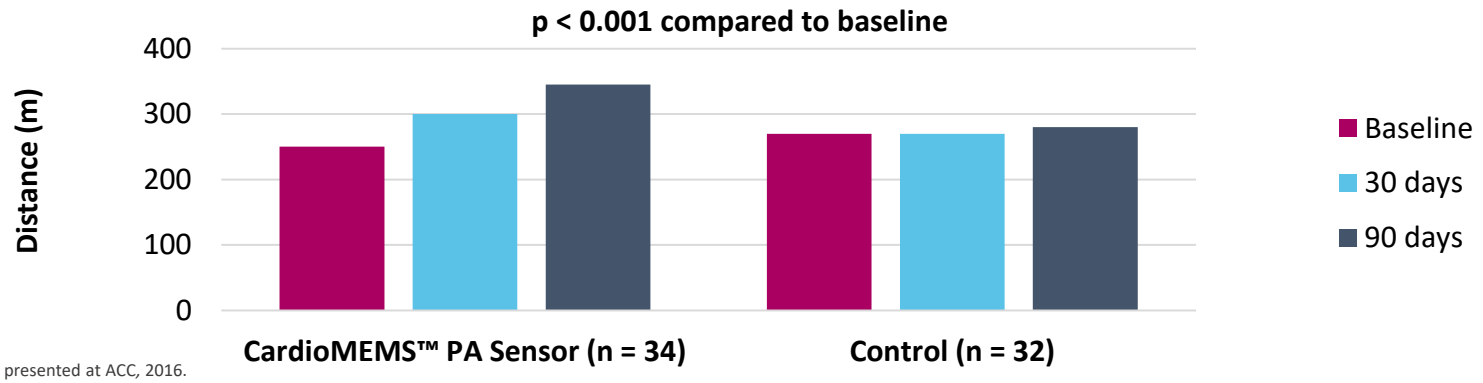
Northwell Health:

SIGNIFICANT IMPROVEMENT IN FC AND QoL IN PATIENTS IMPLANTED WITH THE CardioMEMS™ HF SYSTEM

KCCQ: 3-fold greater improvement in scores



6-minute walk: Avg. increase of 96 meters at 90 days versus no increase in the SoC group



Alam A, et al. Abstract presented at ACC, 2016.

CONCLUDING SUMMARY

- The CardioMEMS™ HF System is safe, reliable and clinically proven in clinical trials and real-world settings.

- It provides a proactive, personalized approach to prevent acute decompensation in both HFrEF and HFpEF patients.

Panel Discussion: Clinical Care Management Studies

Acute Heart Failure, Cardiorenal Syndrome, Evolution to HFpEF

Closing Remarks

Jayne Testa, CMPE

Kettering Heart & Vascular Executive Director