# Heart Failure Management 2019

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# Disclosures

# Summary

- Background of Heart Failure
- 2017 Heart Failure Guidelines Update
- Initiation, Continuation, Switching and Withdrawal of Heart Failure Medical Therapies During Hospitalization
- Device Based Solutions
- What’s New in 2019 and Beyond

# Heart Failure Terminology

- **Heart failure** is a global term for the physiological state in which cardiac output is insufficient for the body's needs. Heart Failure is a condition in which a problem with the structure or function of the heart impairs its ability to supply sufficient blood flow to meet the body's needs.

# Heart Failure Pathophysiology

**Heart failure is caused by any condition which reduces the efficiency of the myocardium leading to overload on the myocardium. Over time the increased workload will produce changes to the heart:**

- Reduced contractility, or force of contraction, due to overloading of the ventricle.
- A reduced stroke volume, as a result of a failure of systole, diastole or both.
- Increased heart rate, stimulated by increased sympathetic activity in order to maintain cardiac output.
- Hypertrophy of the myocardium, caused by the terminally differentiated heart muscle fibers increasing in size in an attempt to improve contractility.
- Enlargement of the ventricles, contributing to the enlargement and spherical shape of the failing heart.

# Heart Failure Statistics

***Prevalence***

- Heart failure (HF) affects an estimated 5.1 million Americans ≥ 20 years of age.
- 400,000 new cases of heart failure are diagnosed in the United States annually.

***Incidence***

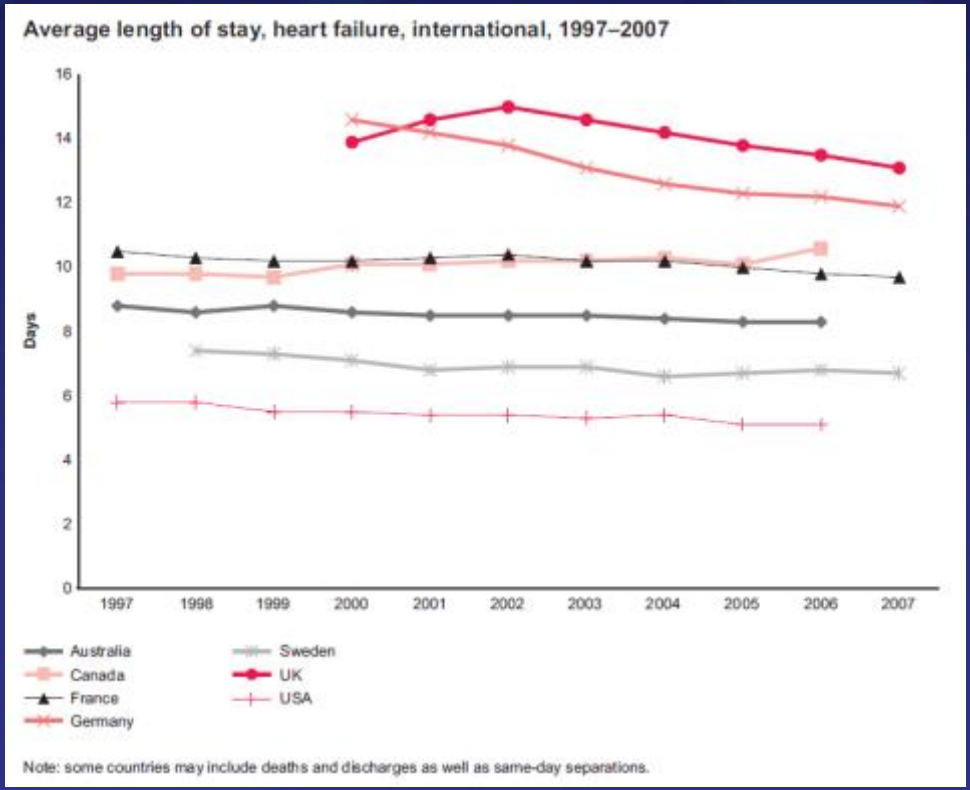
- One-percent of adults 50 to 60 years of age.
- Seventy-five percent of HF cases have antecedent hypertension.
- Ten-percent of adults 80 years of age or older.

***Mortality and Morbidity***

- The lifetime risk for people with BP > 160/90 mmHg is double that of those persons with BP < 140/90 mmHg
- At 40 years of age, the lifetime risk of developing HF for both men and women is 1 in 5; at 80 years of age, the lifetime risk of developing new HF is 20%.
- Most frequent cause of hospitalizations in the elderly and is responsible for 7 to 12 percent of all hospital admissions.
- Contributes to approximately 275,000 deaths every year.

# Heart Failure Is Associated with High Hospitalization and Readmission Rates

- In 2010, there were 1 million hospitalizations in the US with HF as the principal diagnosis[1]
  - Hospitalization rate did not change significantly from 2000[1]
- Average length of hospital stay
  - Approximately 5 days (US)[2]
  - 11 days (Europe)[3]
- HF is also associated with high readmission rates:
  - ~25% all-cause readmission within 30 days and ~50% within 6 months[5]




Graph from www.health.org.uk. Bridging the gap: Heart Failure, 2010.
Data from Organization for Economic Cooperation and Development, 2009.


1. CDC NCHS National Hospital Discharge Survey, 2000-2010
2. Yancy et al. JACC, 2006.
3. Cleland et al. EuroHeart, 2003.
4. Krumholz HM, et al. Circ Cardiovas Qual Outcomes 2009.
5. Wexler DJ, et al. Am Heart J 2001.


Abraham WT, et al. Lancet, 2011.

# Categorization of Heart Failure

**There are many different ways to categorize heart failure, including:**

- Which side of the heart involved (left heart failure versus right heart failure)

- Whether the abnormality is due to contraction (systolic dysfunction) or relaxation of the heart (diastolic)

- Degree of functional impairment conferred by the abnormality (as in the NYHA functional classification)

- Whether the problem is primarily increased venous back pressure (behind) the heart, or failure to supply adequate arterial perfusion (in front of) the heart (backward vs. forward failure)

- Whether the abnormality is due to low cardiac output with high systemic vascular resistance or high cardiac output with low vascular resistance (low-output heart failure vs. high-output heart failure)

# Types of Heart Failure

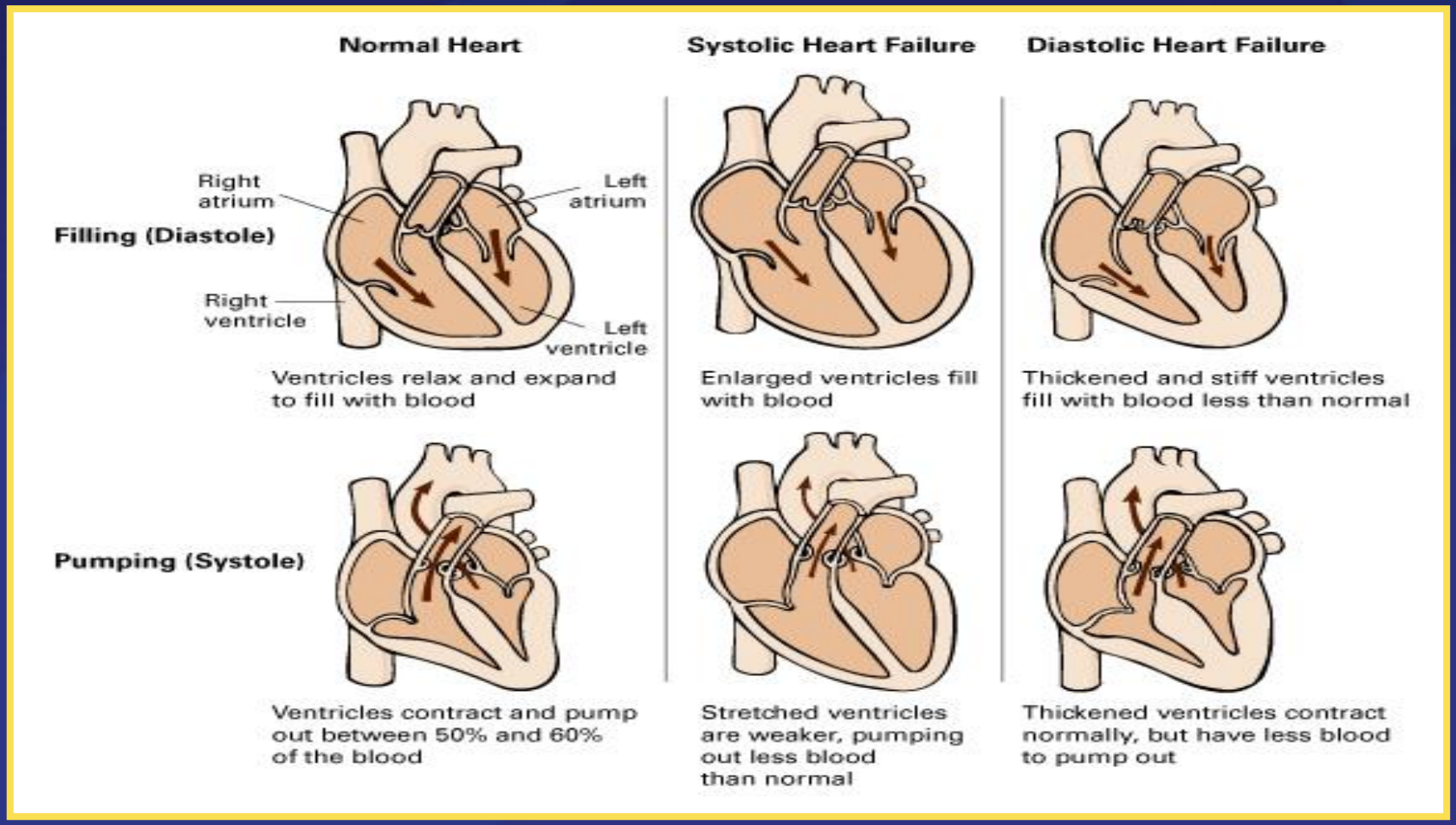
**Classification of heart failure is based on which heart function or which side of the heart is most affected by the condition.**

- ***Systolic heart failure (HFrEF)*** – failure of contraction to pump blood out of the chambers. This is measured by ejection fraction (EF) or the percentage of blood that is ejected out of the ventricle. Normal is 50% or higher.

- ***Diastolic heart failure (HFpEF)*** – failure of relaxation to fill the chambers with blood

# HFrEF and HFpEF

**Each beat of the heart consists of contraction in systole and relaxation in diastole. When the heart contracts, chambers of the heart (ventricles) pump out blood into the lungs and the rest of the body. When the heart relaxes and expands, the ventricles fill completely with blood.**



# Characteristics of HFpEF as Compared with Those of HFrEF

**Table 1. Characteristics of Diastolic Heart Failure as Compared with Those of Systolic Heart Failure.***

| Characteristic | Diastolic Heart Failure | Systolic Heart Failure |
|---|---|---|
| Clinical features | | |
| Symptoms (e.g., dyspnea) | Yes | Yes |
| Congestive state (e.g., edema) | Yes | Yes |
| Neurohormonal activation (e.g., brain natriuretic peptide) | Yes | Yes |
| Left ventricular structure and function | | |
| Ejection fraction | Normal | Decreased |
| Left ventricular mass | Increased | Increased |
| Relative wall thickness† | Increased | Decreased |
| End diastolic volume | Normal | Increased |
| End diastolic pressure | Increased | Increased |
| Left atrial size | Increased | Increased |
| Exercise | | |
| Exercise capacity | Decreased | Decreased |
| Cardiac output augmentation | Decreased | Decreased |
| End diastolic pressure | Increased | Increased |

* The clinical features of diastolic heart failure are similar to those of systolic heart failure, but left ventricular structure and function are distinctly different.

† The descriptor of left ventricular geometry is the relative wall thickness, defined as the ratio of left ventricular wall thickness to the radius of the left ventricular cavity.

# Clues for Differentiating Between HFrEF and HFpEF in Patients with Heart Failure

| Clues from the Evaluation | Systolic Dysfunction HFrEF | Diastolic Dysfunction HFpEF |
|---|---|---|
| **History** | | |
| Hypertension | XX | XXX |
| Coronary Artery Disease* | XXX | XX |
| Diabetes mellitus | XXX | XX |
| Valvular heart disease* | XXX | — |
| **Physical Examination** | | |
| Third heard sound (S3) gallop* | XXX | X |
| Fourth heart sound (S4) gallop | XX | XXX |
| Rales | XX | XX |
| Jugular venous distention | XX | X |
| Edema | XX | X |
| Diplaced point of maximal impulse* | XX | — |
| Mitral regurgitation* | XXX | X |

# Clues for Differentiating Between HFrEF and HFpEF in Patients with Heart Failure

| Clues from the evaluation | HFrEF | HFpEF |
|---|---|---|
| **Chest Radiograph** | | |
| Cardiomegaly* | XXX | X |
| Pulmonary congestion | XXX | XXX |
| **Electrocardiogram** | | |
| Q wave | XX | X |
| Left ventricular hypertrophy* | X | XXX |
| **Echocardiogram** | | |
| Decreased ejection fraction* | XXX | — |
| Dilated left ventricle* | XX | — |
| Left ventricle hypertrophy* | X | XXX |

X = suggestive, the number of Xs reflects the relative weight; — = not suggestive.* and — Particularly helpful in distinguishing systolic from diastolic dysfunction in heart failure.

# NYHA Functional Classification

| Class | Description |
|---|---|
| I (Mild) | No limitation of physical activity - ordinary physical activity doesn't cause tiredness, heart palpitations, or shortness of breath |
| II (Mild) | Slight limitation of physical activity, comfortable at rest, but ordinary physical activity results in tiredness, heart palpitations, or shortness of breath |
| III (Moderate) | Marked or noticeable limitations of physical activity, comfortable at rest, but less than ordinary physical activity causes tiredness, heart palpitations, or shortness of breath |
| IV (Severe) | Severe limitation of physical activity, unable to carry out any physical activity without discomfort. Symptoms also present at rest. If any physical activity is undertaken, discomfort increases. |

# AHA/ACC 2009 - Staging System of Heart

| Stage | Description | Examples |
|---|---|---|
| A | People at high risk for developing heart failure but without structural heart disease or symptoms of heart failure. Encompasses "pre heart failure" where intervention with management can overt Progression to symptoms | CAD (coronary artery disease), diabetes, hypertension, metabolic syndrome, obesity, using cardiotoxins or alcohol, family history of cardiomyopathy, cerebrovascular accident (CVA), personal history of rheumatic fever |
| B | People with structural heart disease but without signs and symptoms of heart failure NYHA Class I | Left ventricular hypertrophy (LVH) or reduced left ventricular ejection fraction (LVEF), asymptomatic valvular heart disease, previous MI |
| C | People with structural heart disease with prior or current symptoms of heart failure NYHA Class II and III | Known structural heart disease with dyspnea, fatigue, inability to exercise |
| D | People who have advanced heart failure and severe symptoms difficult to manage with standard treatment NYHA Class IV | Marked symptoms at rest despite maximal medical therapy, with recurrent hospitalizations |

# 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

Developed in Collaboration With the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation

# Classification of Recommendations and Levels of Evidence

## CLASS (STRENGTH) OF RECOMMENDATION

**CLASS I (STRONG)** — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

**CLASS IIa (MODERATE)** — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

**CLASS IIb (WEAK)** — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

**CLASS III: No Benefit (MODERATE)** — **Benefit = Risk**
*(Generally, LOE A or B use only)*

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

**CLASS III: Harm (STRONG)** — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

## LEVEL (QUALITY) OF EVIDENCE‡

**LEVEL A**
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

**LEVEL B-R (Randomized)**
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

**LEVEL B-NR (Nonrandomized)**
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

**LEVEL C-LD (Limited Data)**
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

**LEVEL C-EO (Expert Opinion)**

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

**This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update**

# Introduction

- The purpose of this focused update is to update the “2013 ACCF/AHA Guideline for the Management of Heart Failure” (2013 HF guideline) in areas where in which new evidence has emerged since its publication.
- 
- The scope of the focused update includes revision to the sections on
  - Biomarkers
  - New therapies indicated for stage CHF with reduced ejection fraction (HF*r*EF)
  - Updates on HF with preserved ejection fraction (HF*p*EF)
  - New data on important comorbidities, including sleep apnea, anemia, and hypertension
  - And new insights regarding the prevention of HF

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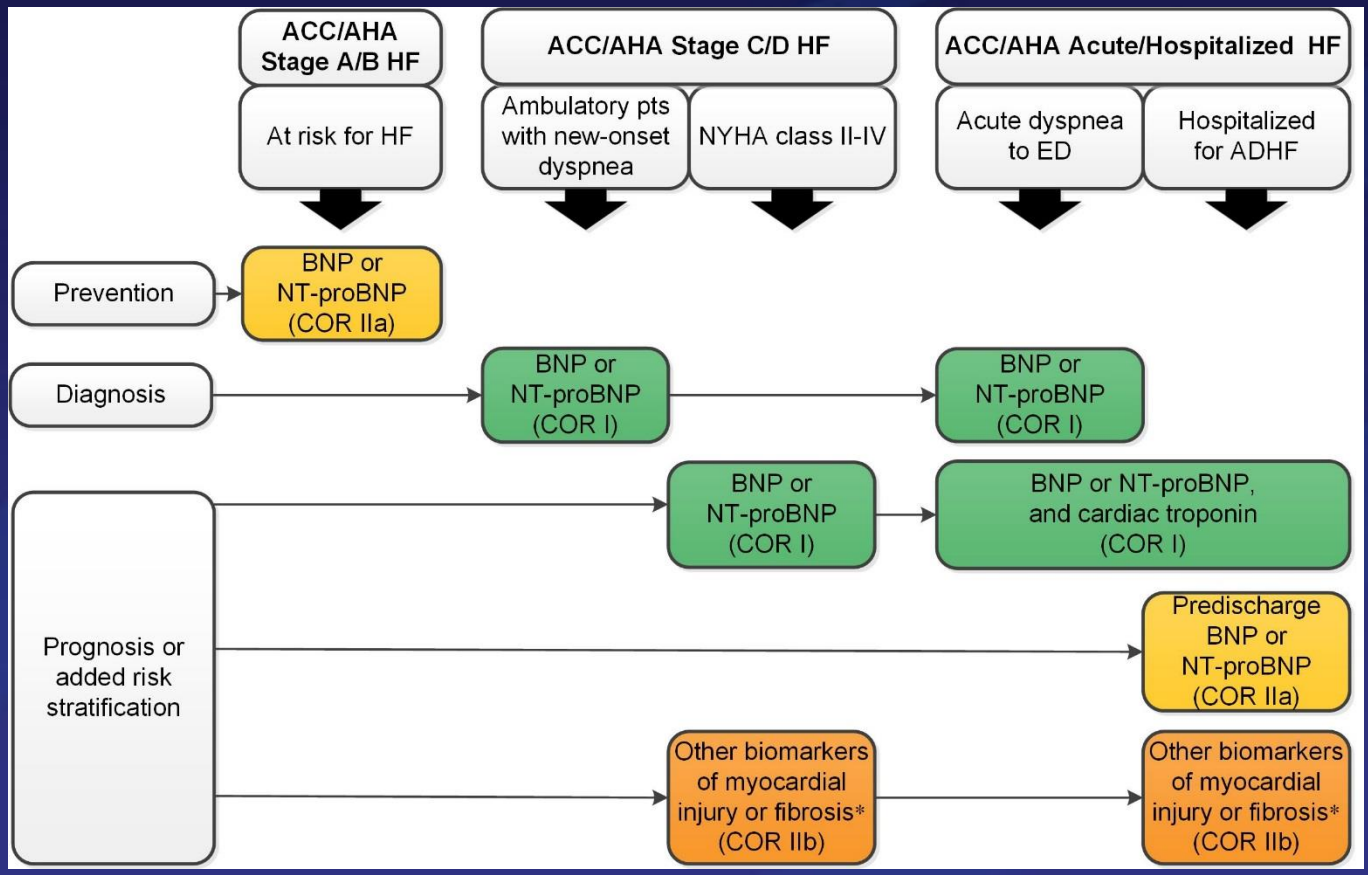
# Initial and Serial Evaluation of Heart Failure

# Initial and Serial Evaluation of Heart Failure

## Biomarkers

# Biomarkers Indications for Use




***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.**

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# Biomarkers

## Biomarkers Indications for Use

| COR | LOE | Recommendation | Comment/ Rationale |
|---|---|---|---|
| IIa | B-R | For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF. | NEW: New data suggest that natriuretic peptide biomarker screening and early intervention may prevent HF. |

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# Biomarkers Indications for Use



Original Investigation

## Natriuretic Peptide–Based Screening and Collaborative Care for Heart Failure

### The STOP-HF Randomized Trial

Mark Ledwidge, PhD; Joseph Gallagher, MB; Carmel Conlon, PhD; Elaine Tallon, PGDip; Eoin O'Connell, MLitt; Ian Dawkins, DPhil; Chris Watson, PhD; Rory O'Hanlon, MD; Margaret Bermingham, BSc(Pharm); Anil Patle, MBA; Mallikarjuna R. Badabhagni, RDCS; Gillian Murtagh, MD; Victor Voon, MB; Leslie Tilson, PhD; Michael Barry, MD; Laura McDonald; Brian Maurer, MD; Kenneth McDonald, MD

**IMPORTANCE** Prevention strategies for heart failure are needed.

**OBJECTIVE** To determine the efficacy of a screening program using brain-type natriuretic peptide (BNP) and collaborative care in an at-risk population in reducing newly diagnosed heart failure and prevalence of significant left ventricular (LV) systolic and/or diastolic dysfunction.

**DESIGN, SETTING, AND PARTICIPANTS** The St Vincent's Screening to Prevent Heart Failure Study, a parallel-group randomized trial involving 1374 participants with cardiovascular risk factors (mean age, 64.8 [SD, 10.2] years) recruited from 39 primary care practices in Ireland between January 2005 and December 2009 and followed up until December 2011 (mean follow-up, 4.2 [SD, 1.2] years).

**INTERVENTION** Patients were randomly assigned to receive usual primary care (control condition; n=677) or screening with BNP testing (n=697). Intervention-group participants with BNP levels of 50 pg/mL or higher underwent echocardiography and collaborative care between their primary care physician and specialist cardiovascular service.

**MAIN OUTCOMES AND MEASURES** The primary end point was prevalence of asymptomatic LV dysfunction with or without newly diagnosed heart failure. Secondary end points included emergency hospitalization for arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or heart failure.

**RESULTS** A total of 263 patients (41.6%) in the intervention group had at least 1 BNP reading of 50 pg/mL or higher. The intervention group underwent more cardiovascular investigations (control, 496 per 1000 patient-years vs intervention, 850 per 1000 patient-years; incidence rate ratio, 1.71; 95% CI, 1.61-1.83; P<.001) and received more renin-angiotensin-aldosterone system–based therapy at follow-up (control, 49.6%; intervention, 56.5%; *P*=.01). The primary end point of LV dysfunction with or without heart failure was met in 59 (8.7%) of 677 in the control group and 37 (5.3%) of 697 in the intervention group (odds ratio [OR], 0.55; 95% CI, 0.37-0.82; *P* = .003). Asymptomatic LV dysfunction was found in 45 (6.6%) of 677 control-group patients and 30 (4.3%) of 697 intervention-group patients (OR, 0.57; 95% CI, 0.37-0.88; *P* = .01). Heart failure occurred in 14 (2.1%) of 677 control-group patients and 7 (1.0%) of 697 intervention-group patients (OR, 0.48; 95% CI, 0.20-1.20; *P* = .12). The incidence rates of emergency hospitalization for major cardiovascular events were 40.4 per 1000 patient-years in the control group vs 22.3 per 1000 patient-years in the intervention

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Supplemental content at jama.com

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https://www.acc.org/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Tools%20and%20Practice%20Support/Quality%20Programs/Heart%20Failure%20Roundtable%202016/Prevention/Pr%204%20Natriuretic%20peptidebased%20screening.pdf?la=en

# Biomarkers

## Biomarkers for Diagnosis

| COR | LOE | Recommendation | Comment/ Rationale |
|---|---|---|---|
| I | A | In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF. | MODIFIED: 2013 acute and chronic recommendations have been combined into a diagnosis section. |

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# Biomarkers

## Biomarkers for Prognosis or Added Risk Stratification

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| I | A | Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF. | 2013 recommendation remains current. |
| I | A | Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF. | MODIFIED: Current recommendation emphasizes that it is admission levels of natriuretic peptide biomarkers that are useful. |

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# Biomarkers

## Biomarkers for Prognosis or Added Risk Stratification

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| IIa | B-NR | During a hospitalization for HF, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis. | NEW: Current recommendation reflects new observational studies. |
| IIb | B-NR | In patients with chronic HF, measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, may be considered for additive risk stratification. | MODIFIED: 2013 recommendations have been combined into prognosis section, resulting in LOE change from A to B-NR. |

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# 2017 Heart Failure Focused Update

## Treatment of HF Stages A Through D

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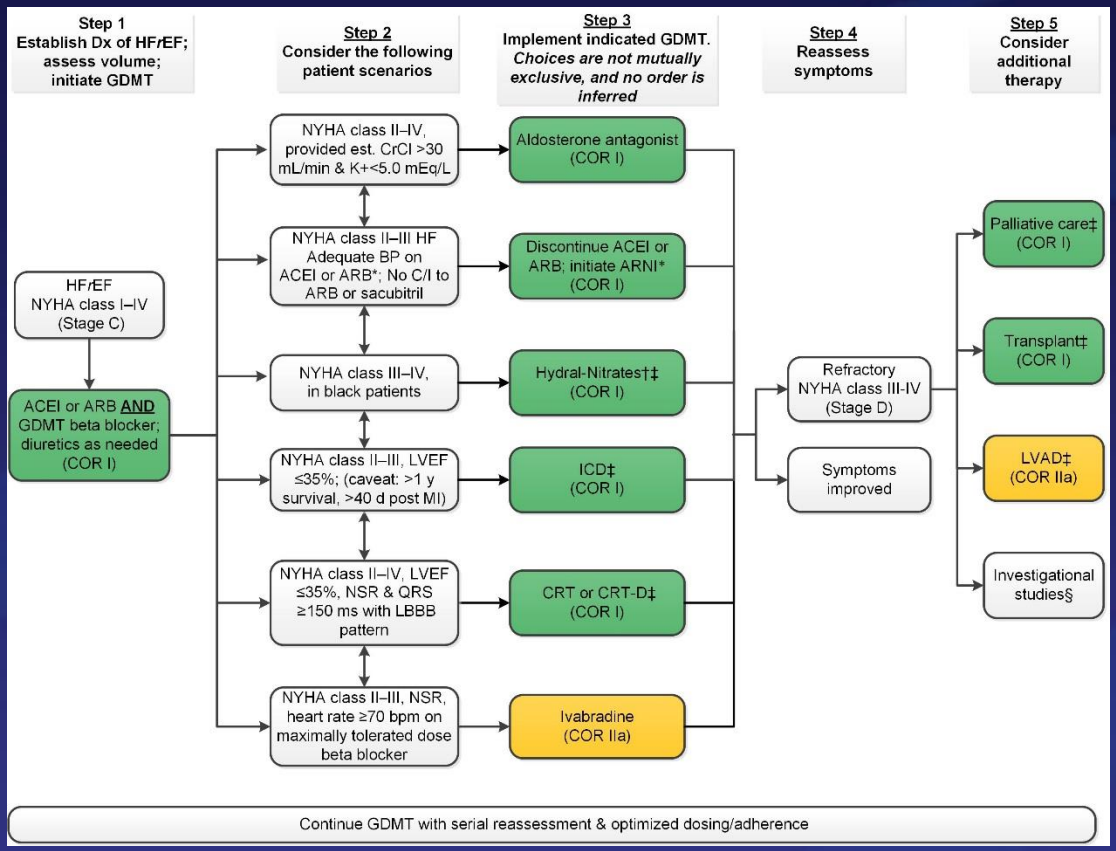
# Treatment of HF Stages A Through D

## Stage C

# Treatment of HFrEF Stage C and D




**†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.**
**§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; HFrEF, 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.**

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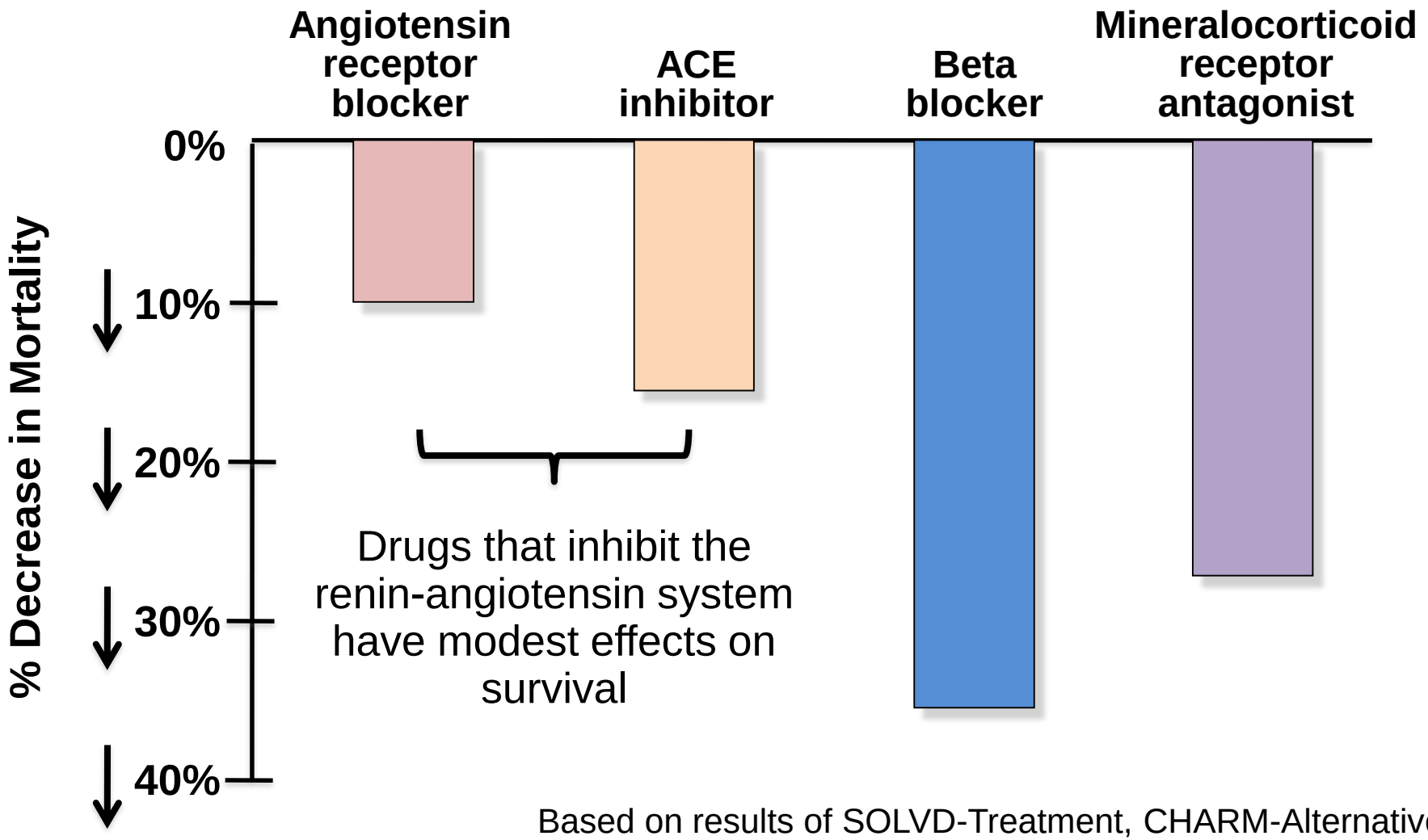
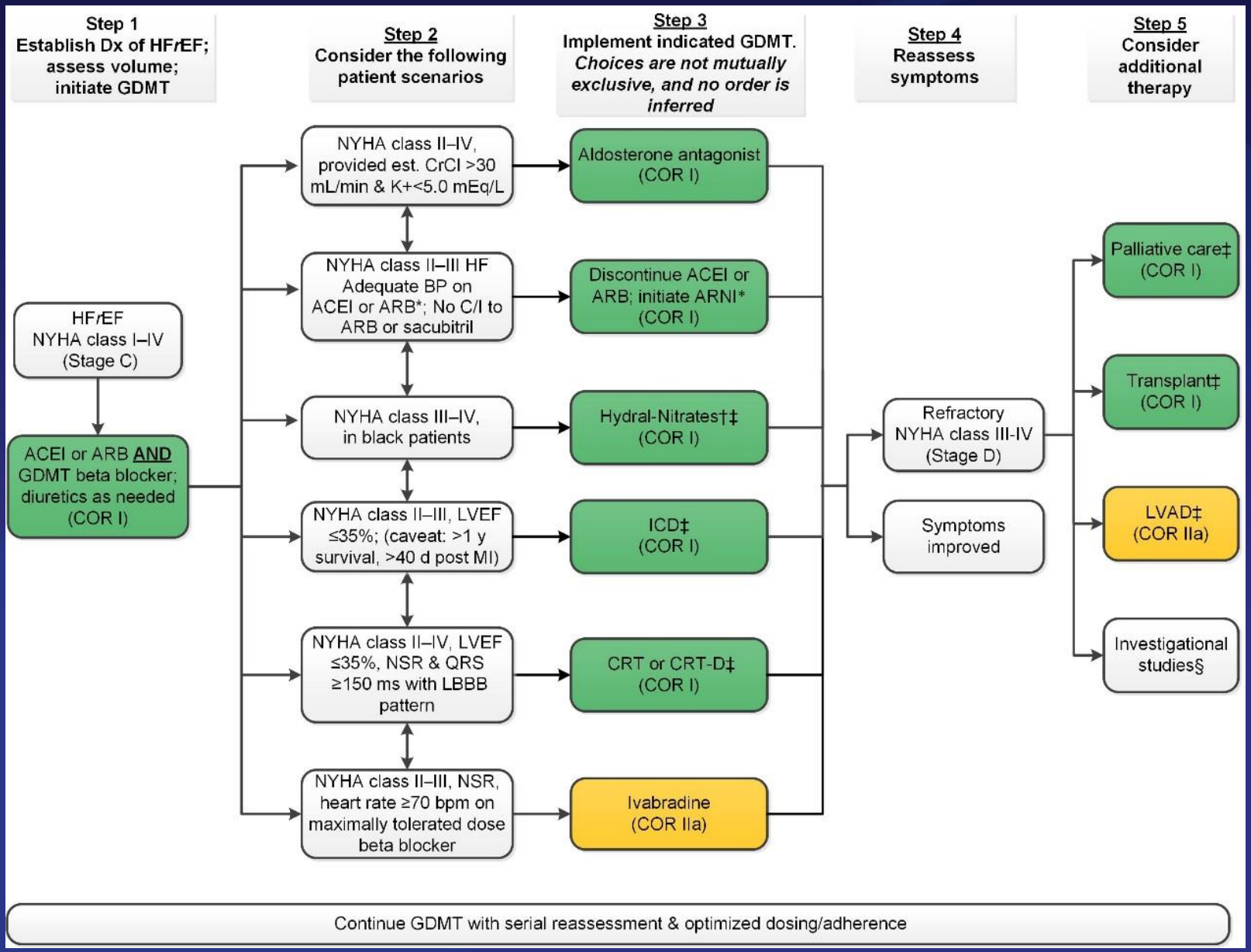
# Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction




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

http://www.clinicaltrialresults.org/Slides/ESC%202014/Packer%20-PARADIGM.ppt

# Treatment of HFrEF Stage C and D

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# Pharmacological Treatment for Stage C HF With Reduced EF

## Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| I | ACE-I: A | The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A), OR ARBs (Level of Evidence: A), OR ARNI (Level of Evidence: B-R) in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality. | NEW: New clinical trial data prompted clarification and important updates. |
| | ARB: A | | |
| | ARNI: B-R | | |

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# Pharmacological Treatment for Stage C HF With Reduced EF

## Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| I | ACE-I: A | The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HF*r*EF to reduce morbidity and mortality. | 2013 recommendation repeated for clarity in this section. |
| I | ARB: A | The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HF*r*EF who are intolerant to ACE inhibitors because of cough or angioedema. | 2013 recommendation repeated for clarity in this section. |

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# Pharmacological Treatment for Stage C HF With Reduced EF

## Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| I | **ARNI: B-R** | In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. | NEW: New clinical trial data necessitated this recommendation. |

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

# Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

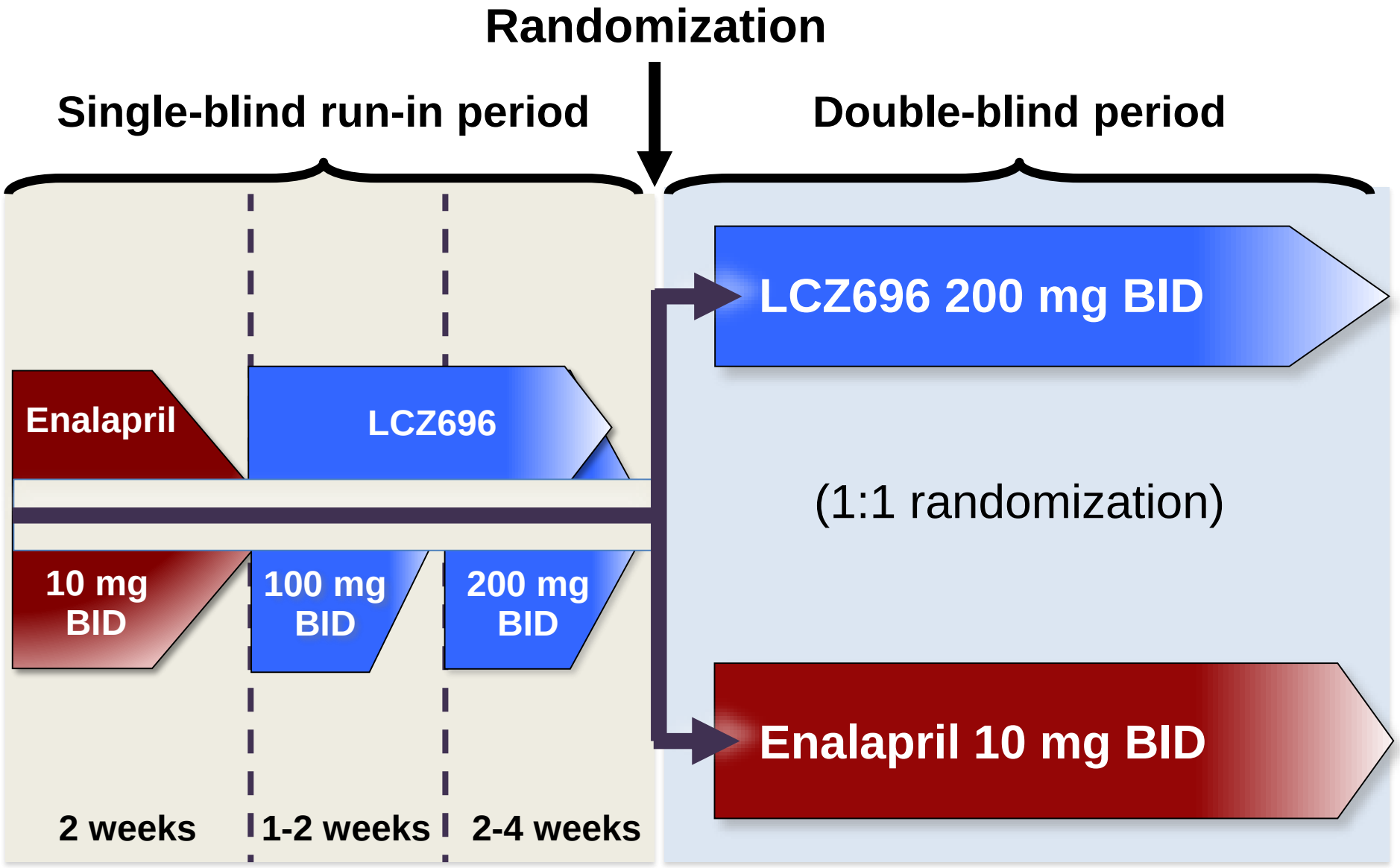
**(all comparisons are versus enalapril 20 mg daily, not versus placebo)**

# How Does it Work?

Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides including natriuretic peptides, bradykinin and adrenomedullin.

Inhibition of neprilysin increases levels of these substances countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention and remodeling

# PARADIGM-HF: Study Design




http://www.clinicaltrialresults.org/Slides/ESC%202014/Packer%20-PARADIGM.ppt

# PARADIGM-HF: Summary of Findings

**In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:**

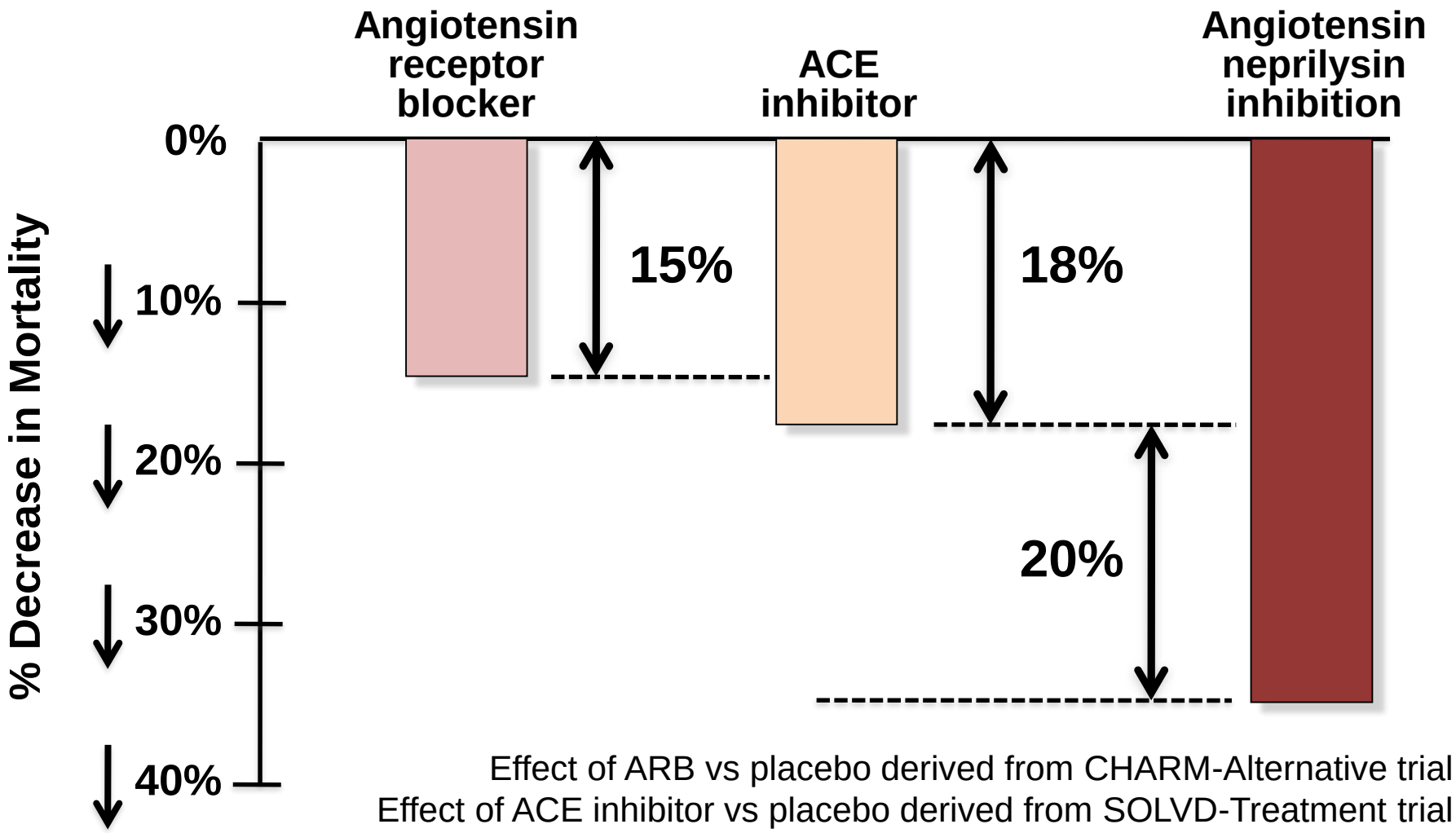
**LCZ696 was *more effective* than enalapril in . . .**

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- *Incrementally* improving symptoms and physical limitations

**LCZ696 was *better tolerated* than enalapril . . .**

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

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




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

http://www.clinicaltrialresults.org/Slides/ESC%202014/Packer%20-PARADIGM.ppt

# Pharmacological Treatment for Stage C HF With Reduced EF

## Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| **III: Harm** | **B-R** | ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. | NEW: Available evidence demonstrates a potential signal of harm for a concomitant use of ACE inhibitors and ARNI. |
| **III: Harm** | **C-EO** | ARNI should not be administered to patients with a history of angioedema. | NEW: New clinical trial data. |

**This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update**

# Pharmacological Treatment for Stage C HF With Reduced EF

## Ivabradine

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| IIa | B-R | Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (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. | NEW: New clinical trial data. |

*In other parts of the document, the term "GDMT" has been used to denote guideline-directed management and therapy. In this recommendation, however, the term "GDEM" has been used to denote this same concept in order to reflect the original wording of the recommendation that initially appeared in the "2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure".

This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update

# Pharmacological Treatment for Stage C HF With Preserved EF

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| I | B | Systolic and diastolic blood pressure should be controlled in patients with HF*p*EF in accordance with published clinical practice guidelines to prevent morbidity | 2013 recommendation remains current. |
| I | C | Diuretics should be used for relief of symptoms due to volume overload in patients with HF*p*EF. | 2013 recommendation remains current. |

This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update

# Pharmacological Treatment for Stage C HF With Preserved EF

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| IIa | C | Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HF*p*EF despite GDMT. | 2013 recommendation remains current. |
| IIa | C | Management of AF according to published clinical practice guidelines in patients with HF*p*EF is reasonable to improve symptomatic HF. | 2013 recommendation remains current. |
| IIa | C | The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HF*p*EF. | 2013 recommendation remains current. |

This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update

# Pharmacological Treatment for Stage C HF With Preserved EF

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| IIb | B-R | In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations. | NEW: Current recommendation reflects new RCT data. |
| IIb | B | The use of ARBs might be considered to decrease hospitalizations for patients with HF*p*EF. | 2013 recommendation remains current. |

This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update

# Pharmacological Treatment for Stage C HF With Preserved EF

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| **III: No Benefit** | **B-R** | Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HF*p*EF is ineffective. | NEW: Current recommendation reflects new data from RCTs. |
| **III: No Benefit** | **C** | Routine use of nutritional supplements is not recommended for patients with HF*p*EF. | 2013 recommendation remains current. |

**This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update**

# 2017 Heart Failure Focused Update

## Important Comorbidities in HF

# Important Comorbidities in HF

## Anemia

# Anemia

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| **IIb** | **B-R** | 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. | NEW: New evidence consistent with therapeutic benefit. |
| **III: No Benefit** | **B-R** | In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality. | NEW: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit. |

**This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update**

# Iron Deficiency in Heart Failure

- At present, intravenous (IV) iron is the preferred route for treatment in heart failure patients. Most studies have used IV iron sucrose (maximum dose of 200 mg per setting) or ferric carboxymaltose (maximum dose of 1000 mg per week).

- Multiple placebo-controlled, randomized clinical trials have been conducted with IV iron in patients with New York Heart Association class II-III heart failure with an ejection fraction ≤45% who met criteria for iron deficiency, *regardless of whether anemia was present.* IV iron administration was associated with improvement in patient-reported outcomes and functional capacity. However, these trials did not examine the impact of IV iron on mortality and hospitalizations.

- To date, no clinical trial has proven the efficacy of oral iron in patients with heart failure with reduced ejection fraction. Furthermore, oral iron preparations are associated with a high incidence of adverse effects (in up to 40% of patients), are poorly absorbed due to gut wall edema, and can take up to 6 months to replenish iron stores.

https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2018/12/31/20/40/iron-deficiency-in-heart-failure

# Important Comorbidities in HF

## Hypertension

# Hypertension

## Treating Hypertension to Reduce the Incidence of HF

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| I | B-R | In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg. | NEW: Recommendation reflects new RCT data. |

**This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update**

# Hypertension

## Treating Hypertension in Stage C HF*r*EF

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| I | C-EO | Patients with HF*r*EF and hypertension should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg. | NEW: Recommendation has been adapted from recent clinical trial data but not specifically tested per se in a randomized trial of patients with HF. |

This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update

# Hypertension

## Treating Hypertension in Stage C HF*p*EF

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| I | C-LD | Patients with HF*p*EF and persistent hypertension after management of volume overload should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg. | NEW: New target goal blood pressure based on updated interpretation of recent clinical trial data. |

This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update

# Important Comorbidities in HF

## Sleep Disorders

# Sleep Disorders

| COR | LOE | Recommendations | Comment/ Rationale |
|---|---|---|---|
| **IIa** | **C-LD** | In patients with NYHA class II–IV HF and suspicion of sleep disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable. | NEW: Recommendation reflects clinical necessity to distinguish obstructive versus central sleep apnea. |
| **IIb** | **B-R** | In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness. | NEW: New data demonstrate the limited scope of benefit expected from CPAP for obstructive sleep apnea. |
| **III: Harm** | **B-R** | In patients with NYHA class II–IV HF*r*EF and central sleep apnea, adaptive servo-ventilation causes harm. | NEW: New data demonstrate a signal of harm when adaptive servo-ventilation is used for central sleep apnea. |

**This slide set was adapted from the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (*Journal of the American College of Cardiology).* Published on April 28, 2017, available at: Yancy, et. al. ACC/AHA/HFSA 2017 Heart Failure Focused Update**

# Management of Acute Decompensated Heart Failure

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

ABSTRACT

**BACKGROUND**

Acute decompensated heart failure accounts for more than 1 million hospitalizations in the United States annually. Whether the initiation of sacubitril–valsartan therapy is safe and effective among patients who are hospitalized for acute decompensated heart failure is unknown.

**METHODS**

We enrolled patients with heart failure with reduced ejection fraction who were hospitalized for acute decompensated heart failure at 129 sites in the United States. After hemodynamic stabilization, patients were randomly assigned to receive sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or enalapril (target dose, 10 mg twice daily). The primary efficacy outcome was the time-averaged proportional change in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration from baseline through weeks 4 and 8. Key safety outcomes were the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema.

**RESULTS**

Of the 881 patients who underwent randomization, 440 were assigned to receive sacubitril–valsartan and 441 to receive enalapril. The time-averaged reduction in the NT-proBNP concentration was significantly greater in the sacubitril–valsartan group than in the enalapril group; the ratio of the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53 in the sacubitril–valsartan group as compared with 0.75 in the enalapril group (percent change, −46.7% vs. −25.3%; ratio of change with sacubitril–valsartan vs. enalapril, 0.71; 95% confidence interval [CI], 0.63 to 0.81; P<0.001). The greater reduction in the NT-proBNP concentration with sacubitril–valsartan than with enalapril was evident as early as week 1 (ratio of change, 0.76; 95% CI, 0.69 to 0.85). The rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups.

**CONCLUSIONS**

Among patients with heart failure with reduced ejection fraction who were hospi-

From the Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT (E.J.V.); the Thrombolysis in Myocardial Infarction Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston (D.A.M., E.B.); Duke Clinical Research Institute, Duke University, Durham, NC (A.D.D.); Novartis Pharmaceuticals, East Hanover, NJ (C.I.D., K.M., R.R.); and the Division of Cardiology, Permanente Medical Group, San Francisco, and the Division of Research, Kaiser Permanente Northern California, Oakland — both in California (A.P.A.). Address reprint requests to Dr. Velazquez at Yale University School of Medicine, P.O. Box 208017, New Haven, CT 06520-8017, or at eric.velazquez@yale.edu.

*A complete list of the PIONEER-HF investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 11, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1812851



https://scaci.org/_files/aha2018/PIONEER-HF-art%C3%ADculo-original.pdf

# Angiotensin Receptor-Neprilysin Inhibition in Patients Hospitalized With Acute Decompensated Heart Failure

Eric J Velazquez,[1] David A Morrow,[2] Adam D DeVore,[3] Carol I Duffy,[4] Andrew P Ambrosy,[3] Kevin McCague,[4] Ricardo Rocha,[4] Eugene Braunwald[2]

# Background

- Acute decompensated heart failure (ADHF) accounts for over 1M hospitalizations in the US annually

- Guideline-directed therapy for ADHF is limited
  - Decongestion with diuretics and hemodynamic support with vasodilators remain the standards of care

# Rationale

- PARADIGM-HF trial in chronic HFrEF: sacubitril/valsartan ➔ ↓ CV death or HF hospitalization compared to enalapril
  - Patients with ADHF requiring IV therapy were excluded
  - Stable HF therapy with adequate doses for >4 weeks
  - Required sequential run-in with high dose enalapril and sacubitril/valsartan before randomization

- It is unknown if in-hospital initiation of sacubitril/valsartan compared to enalapril is safe and effective in ADHF

McMurray JJ. *NEJM*. 2014;371:993-1004.

# Conclusions

Among hemodynamically stabilized acute heart failure patients with reduced EF, compared with enalapril, sacubitril/valsartan administered over 8 weeks

- Led to greater reduction in NT-proBNP
- Reduced re-hospitalization for heart failure
- Was well tolerated with comparable rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema

McMurray JJ. *NEJM*. 2014;371:993-1004.

# Clinical Implications

These results support the in-hospital initiation of sacubitril/valsartan in stabilized patients with acute decompensated heart failure and reduced EF, irrespective of prior ACEi/ARB use, or prior HF diagnosis.

McMurray JJ. *NEJM*. 2014;371:993-1004.

# Heart Failure Therapies During Hospitalization

JACC: Heart Failure

Volume 7, Issue 1, January 2019
DOI: 10.1016/j.jchf.2018.06.011

PDF Article

## Initiation, Continuation, Switching, and Withdrawal of Heart Failure Medical Therapies During Hospitalization

Aditi A. Bhagat, Stephen J. Greene, Muthiah Vaduganathan, Gregg C. Fonarow and Javed Butler



https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/01/10/13/56/initiation-continuation-switching-and-withdrawal

# Heart Failure Therapies During Hospitalization

Hospitalization in patients with heart failure and reduced ejection fraction (HFrEF) provides a key opportunity to re-address guideline-directed medical therapies (GDMT). Pre-discharge initiation of GDMT is associated with improved rates of post-discharge use.

https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/01/10/13/56/initiation-continuation-switching-and-withdrawal

# Heart Failure Therapies During Hospitalization

Landmark trials with beta-blockers in HFrEF patients showed that they were safely tolerated with a low risk for deterioration and demonstrated an early mortality benefit by week 8 of initiation. Small randomized trials suggest that pre-discharge initiation of low-dose beta-blockers in *hemodynamically stable patients* was well tolerated and reduced re-hospitalization and improved functional status at 6 months. Switching from nonevidence-based beta-blockers to evidence-based beta-blockers has not been studied, but based on clinical experience, is well tolerated.

https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/01/10/13/56/initiation-continuation-switching-and-withdrawal

# Heart Failure Therapies During Hospitalization

Observational studies show that continuation of beta-blockers during HFrEF hospitalization is associated with lower risk for re-hospitalization and post-discharge mortality. Withdrawal or dose reduction of beta-blockers should be considered in patients with hemodynamic intolerance, borderline perfusion, cardiogenic shock, or inotrope requirement. Careful attention should be paid to patients with bradycardia due to risk for progression to heart block and tachycardia, which may be a compensatory mechanism for low stroke volume.

https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/01/10/13/56/initiation-continuation-switching-and-withdrawal

# Heart Failure Therapies During Hospitalization

There are no randomized data assessing in-hospital initiation or continuation of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin-receptor blocker (ARB). However, observational studies suggest that in-hospital initiation of ACEI/ARB correlate with lower 30-day re-hospitalization and mortality rates, which persist at 12 months as well.

https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/01/10/13/56/initiation-continuation-switching-and-withdrawal

# Heart Failure Therapies During Hospitalization

Similarly, in-hospital continuation of ACEI/ARB was associated with lower post-discharge mortality and re-hospitalization. Common reasons for their discontinuation are hyperkalemia and renal dysfunction. In particular, caution should be used in initiating ACEI/ARB in hypovolemic patients, as this may be associated with hypotension.

https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/01/10/13/56/initiation-continuation-switching-and-withdrawal

# Heart Failure Therapies During Hospitalization

Benefits of angiotensin receptor/neprilysin inhibitor (ARNI) therapy over ACEI are consistent across a wide spectrum of patients with HFrEF including patients with recent hospitalizations. This suggests clinical benefit with in-hospital switching from ACEI/ARB to ARNI. Inpatient initiation of ARNI therapy in euvolemic patients tolerating ACEI/ARB can be considered and will increase rates of post-discharge use. ACEI must be held for 36 hours prior to ARNI initiation and ARNI should not be used in patients with prior hypersensitivity or angioedema to ACEI/ARB.

https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/01/10/13/56/initiation-continuation-switching-and-withdrawal

# Heart Failure Therapies During Hospitalization

Smaller trials with spironolactone show in-hospital initiation is associated with reduced rates for arrhythmia and greater congestion relief. These benefits have not been consistently demonstrated in observational studies, likely due to confounding with selection bias. In-hospital initiation of spironolactone correlates with higher post-discharge adherence. However, subgroup analysis of a randomized trial showed that patients initiated or continued on spironolactone had a lower 30-day mortality.

https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/01/10/13/56/initiation-continuation-switching-and-withdrawal

# Heart Failure Therapies During Hospitalization

Reasons for low use rates of spironolactone therapy at hospital discharge are not well understood. Nonetheless, based on randomized data, their safety profile has been favorable. Patients who are unable or unwilling to comply with post-discharge clinical and laboratory monitoring should not be considered for initiation or up-titration of spironolactone.

https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/01/10/13/56/initiation-continuation-switching-and-withdrawal

# Heart Failure Therapies During Hospitalization

Patients in the hospital with HFrEF should be counseled and educated regarding need for GDMT and anticipated side effects. Close follow-up after discharge with lab monitoring is mandatory, especially in treatment-naïve patients.

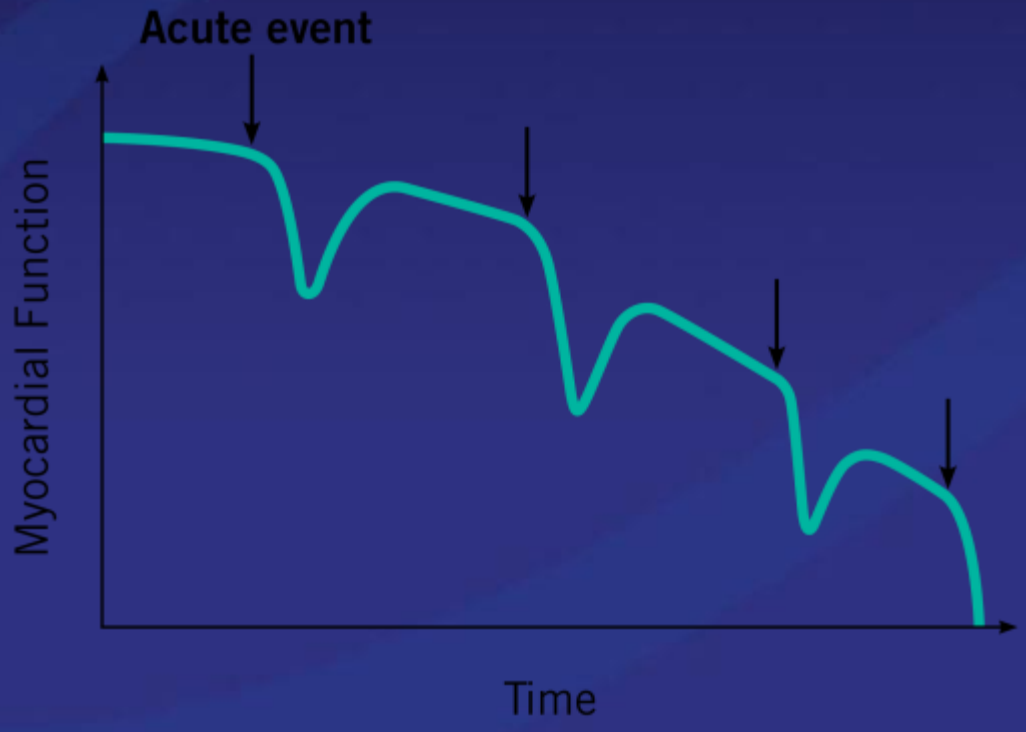
https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/01/10/13/56/initiation-continuation-switching-and-withdrawal

# Hemodynamic Monitoring for Heart Failure Management

- Managing Pressures in the Heart Failure Patient
- CardioMEMS™ HF System
- CHAMPION Clinical Trial

# Worsening Heart Failure Leading to HF Hospitalizations Contributes to Disease Progression

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

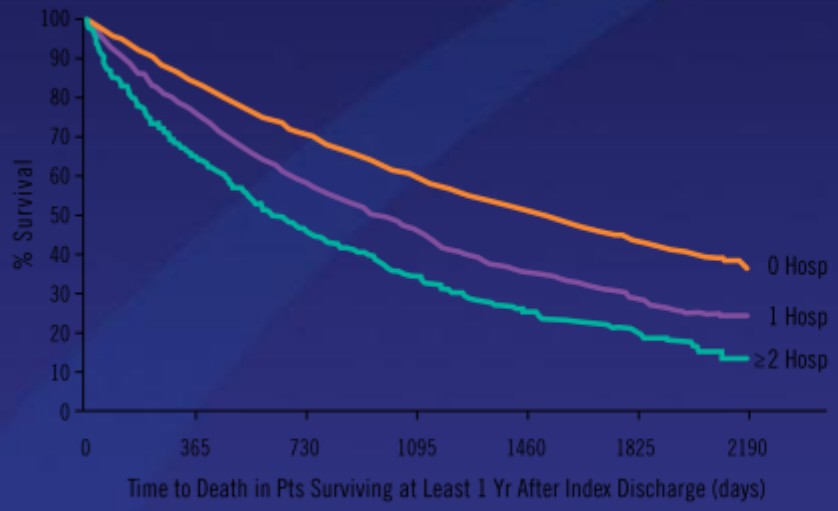



Graph adapted from: Gheorghiade MD, et al. Am J. Cardiol. 2005

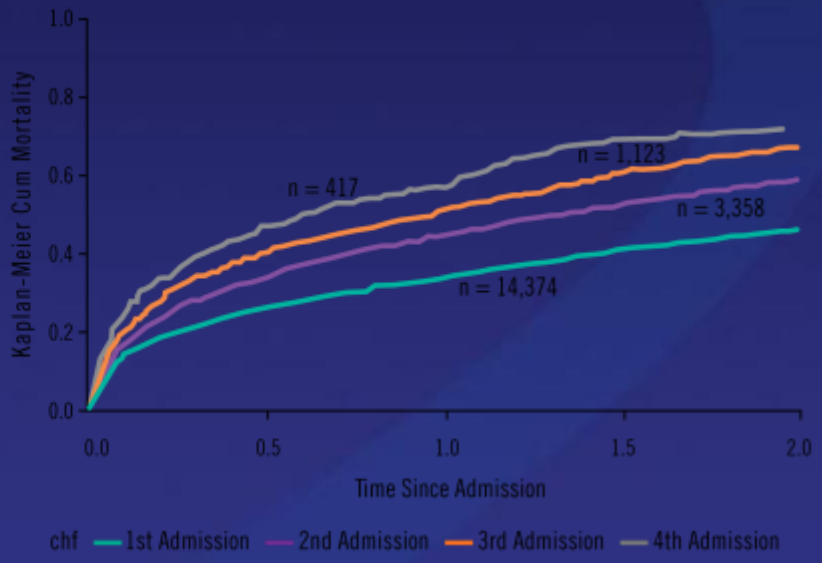
Abraham WT, et al. Lancet, 2011.

# HF Hospitalizations are a Strong Predictor of Mortality[1,2]

- Data from the EFFECT study, n = 9138 patients[1]




- Data from the Setoguchi et al., n = 14,374 patients[2]

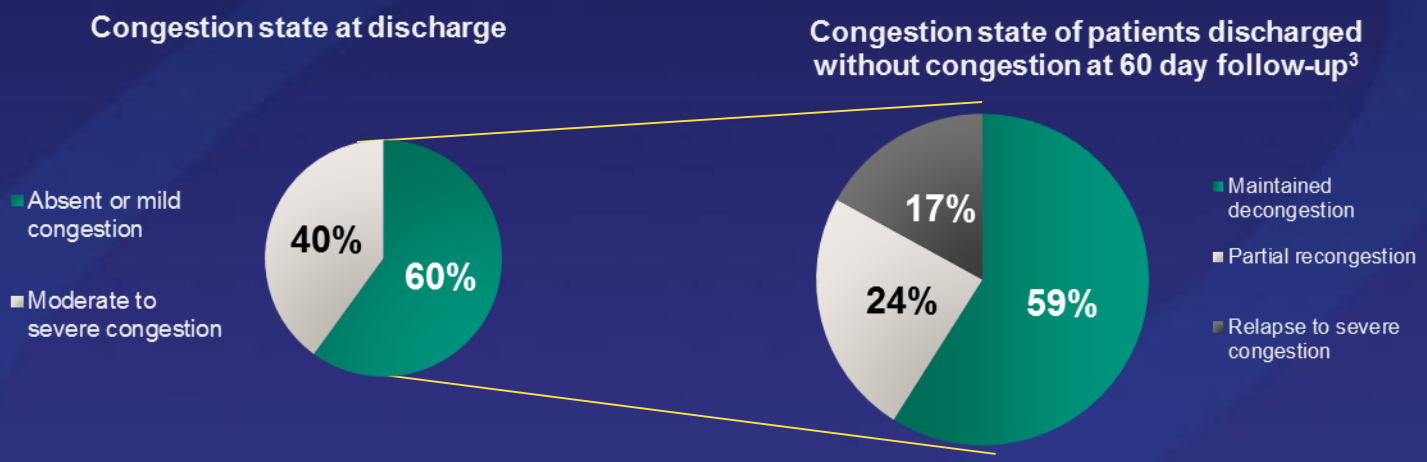



**Studies show each admission decreases a patient's chance of survival.**


1. Lee DS, et al. Am J of Med, 2009.
2. Setoguchi S, et al. Am Heart J, 2007.

# How well do our current tools work?

**1,000,000 hospitalizations for heart failure**
**>3,000,000 hospitalizations include heart failure as contributor**
**25% of patients are readmitted in 30 days 50% in 6 months**

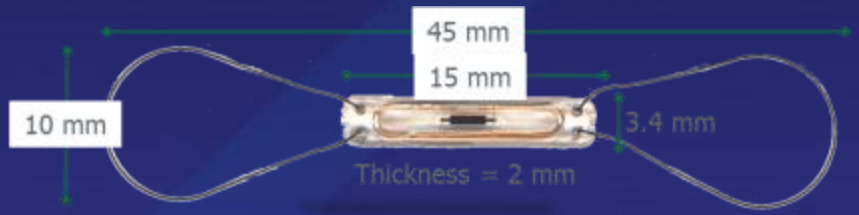



- Post hoc analysis of 463 acute decompensated HF patients from DOSE-HF and CARRESS-HF trials showed:
  - 40% of patients are discharged with moderate to severe congestion.[1]
  - Of patients decongested at discharge, 41% had severe or partial re-congestion by 60 days.[1]

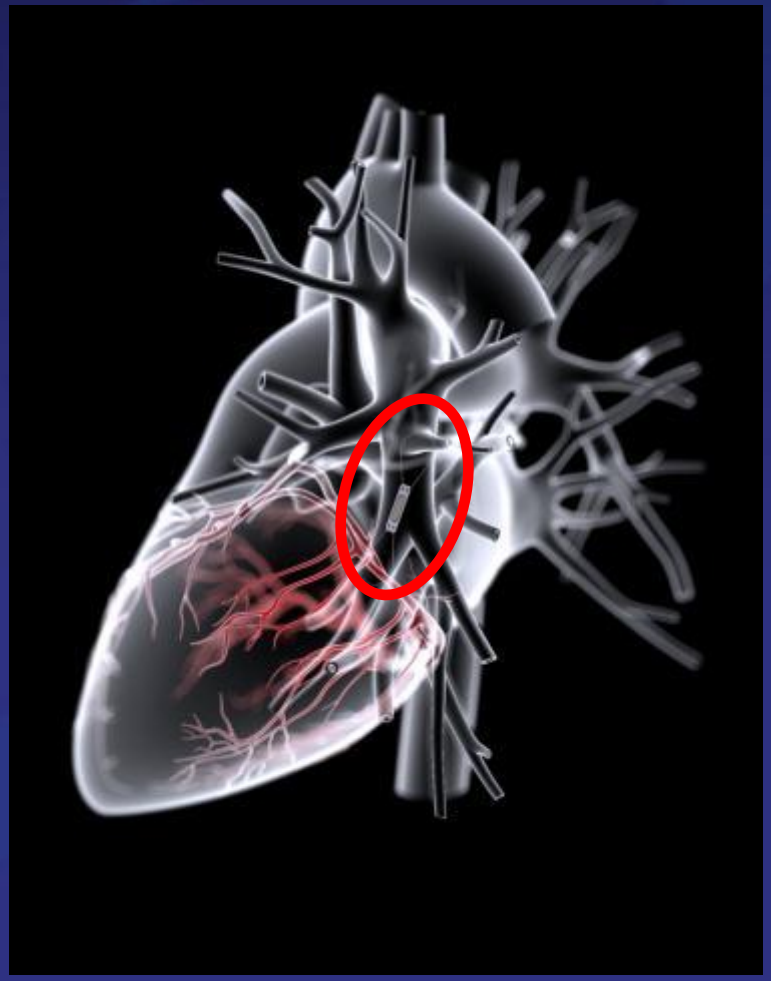
1. Lala A, et al. JCF 2013

# CardioMEMS™ HF System

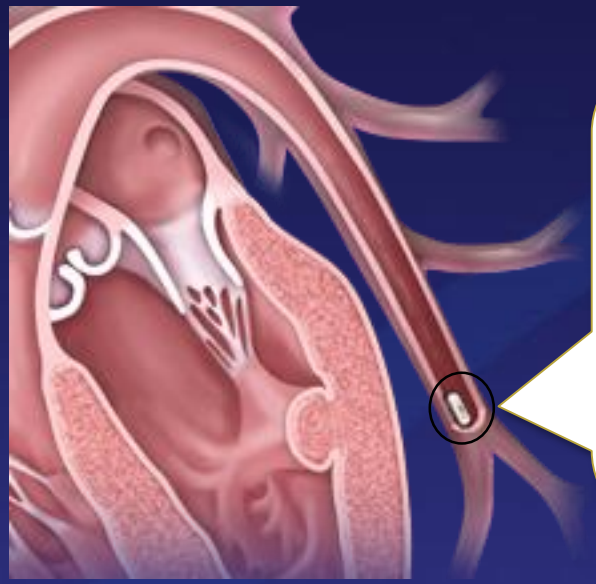
**The pulmonary artery pressure sensor is implanted via a right heart catheterization procedure via femoral vein approach.**



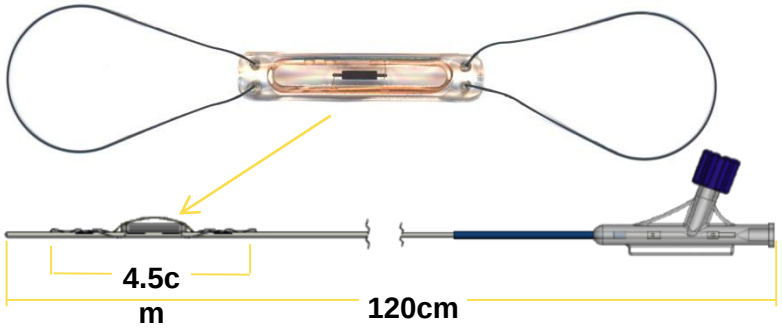

**Target location for pulmonary artery pressure sensor**



# Cardiomems™ HF System

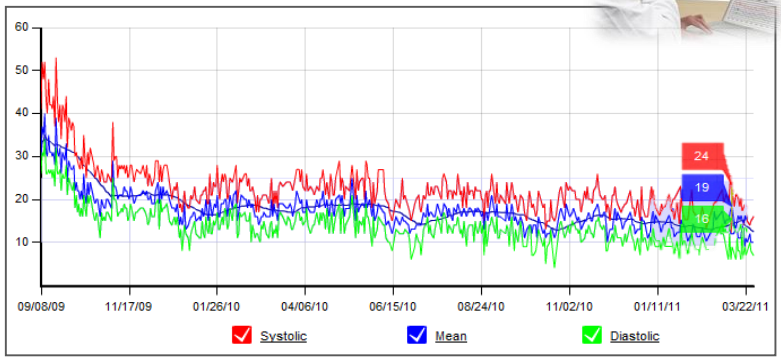


## PA Pressure Sensor on Catheter Delivery System



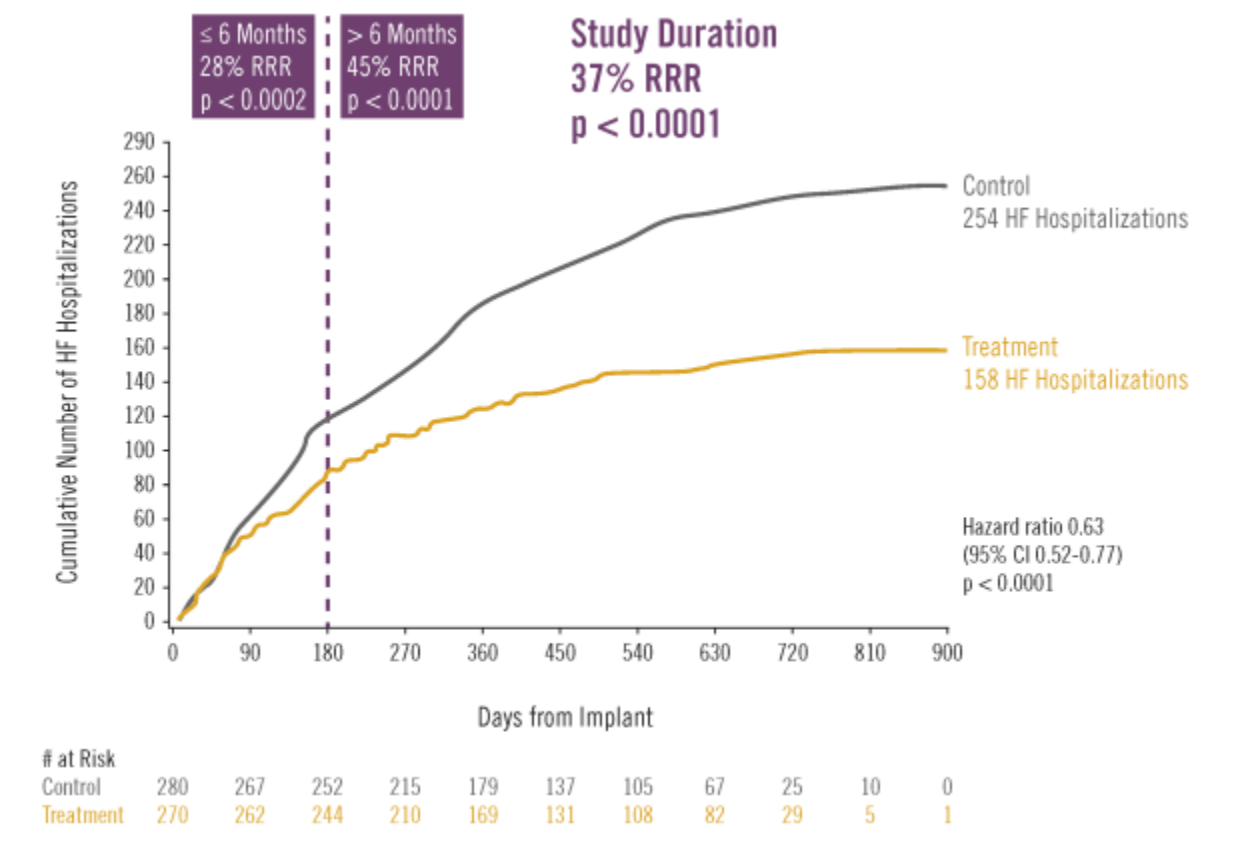

## Patient Home Electronics Unit

## PA Pressure Database




Physician Access Via Secure Website

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




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

Abraham WT, et al. Lancet, 2011.

# What's New in HF in 2019

Meeting Coverage > ESC

## Entresto Signals Expansion Into 'Gray Zone' of HFpEF

— PARAGON-HF may have missed overall, but HF docs see reason for hope

PARIS -- Sacubitril/valsartan (Entresto) struck out on heart failure with preserved ejection fraction (HFpEF) in the PARAGON-HF trial but signaled benefit in the lower range of EF.

Among patients with an EF of 45% or higher, the drug failed to reduce hospitalization for heart failure and death from cardiovascular causes compared with valsartan alone (risk ratio 0.87, 95% CI 0.75-1.01, *P*=0.06), reported Scott Solomon, MD, of Brigham and Women's Hospital and Harvard in Boston.

https://www.medpagetoday.com/meetingcoverage/esc/81922

# What's New in HF in 2019

Meeting Coverage > ESC

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Secondary endpoints favoring sacubitril/valsartan:

NYHA class improved significantly more (15.0% vs 12.6%, OR 1.45, 95% CI 1.13-1.86)
Renal function worsened less (1.4% vs 2.7%, HR 0.50, 95% CI 0.33-0.77)
Health status improved by 1 point on the 100-point KCCQ clinical summary score at 8 months (95% CI 0.0-2.1)

Also, there were two among 12 prespecified groups with possible sacubitril/valsartan benefit for the primary composite endpoint:

Women (RR 0.73, 95% CI 0.59-0.90)
Lower EF for those ≤median of 57% (RR 0.78, 95% CI 0.64-0.95)

https://www.medpagetoday.com/meetingcoverage/esc/81922

# What's New in HF in 2019

## SGLT2 Inhibitors

# What's New in HF in 2019

Circulation

ORIGINAL RESEARCH ARTICLE

## Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus

### Results From the CANVAS Program

**BACKGROUND:** Canagliflozin is a sodium glucose cotransporter 2 inhibitor that reduces the risk of cardiovascular events. We report the effects on heart failure (HF) and cardiovascular death overall, in those with and without a baseline history of HF, and in other participant subgroups.

**METHODS:** The CANVAS Program (Canagliflozin Cardiovascular Assessment Study) enrolled 10 142 participants with type 2 diabetes mellitus and high cardiovascular risk. Participants were randomly assigned to canagliflozin or placebo and followed for a mean of 188 weeks. The primary end point for these analyses was adjudicated cardiovascular death or hospitalized HF.

**RESULTS:** Participants with a history of HF at baseline (14.4%) were more frequently women, white, and hypertensive and had a history of prior cardiovascular disease (all $P<0.001$). Greater proportions of these patients were using therapies such as blockers of the renin angiotensin aldosterone system, diuretics, and β-blockers at baseline (all $P<0.001$). Overall, cardiovascular death or hospitalized HF was reduced in those treated with canagliflozin compared with placebo (16.3 versus 20.8 per 1000 patient-years; hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.67–0.91), as was fatal or hospitalized HF (HR, 0.70; 95% CI, 0.55–0.89) and hospitalized HF alone (HR, 0.67; 95% CI, 0.52–0.87). The benefit on cardiovascular death or hospitalized HF may be greater in patients with a prior history of HF (HR, 0.61; 95% CI, 0.46–0.80) compared with those without HF at baseline (HR, 0.87; 95% CI, 0.72–1.06; $P$ interaction =0.021). The effects of canagliflozin compared with placebo on other cardiovascular outcomes and key safety outcomes were similar in participants with and without HF at baseline (all interaction $P$ values >0.130), except for a possibly reduced absolute rate of events attributable to osmotic diuresis among those with a prior history of HF ($P$=0.03).

**CONCLUSIONS:** In patients with type 2 diabetes mellitus and an elevated risk of cardiovascular disease, canagliflozin reduced the risk of cardiovascular death or hospitalized HF across a broad range of different patient subgroups. Benefits may be greater in those with a history of HF at baseline.

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**Vlado Perkovic, MBBS, PhD**
**Scott D. Solomon, MD**
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**Bruce Neal, MB, ChB, PhD**

*Drs Rådholm and Figtree contributed equally as first authors.

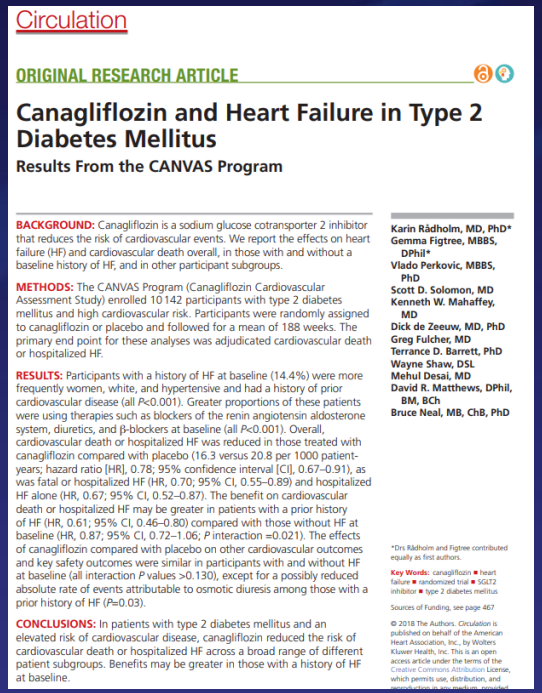
**Key Words:** canagliflozin ■ heart failure ■ randomized trial ■ SGLT2 inhibitor ■ type 2 diabetes mellitus

Sources of Funding, see page 467



https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.118.034222

# What's New in HF in 2019



Circulation

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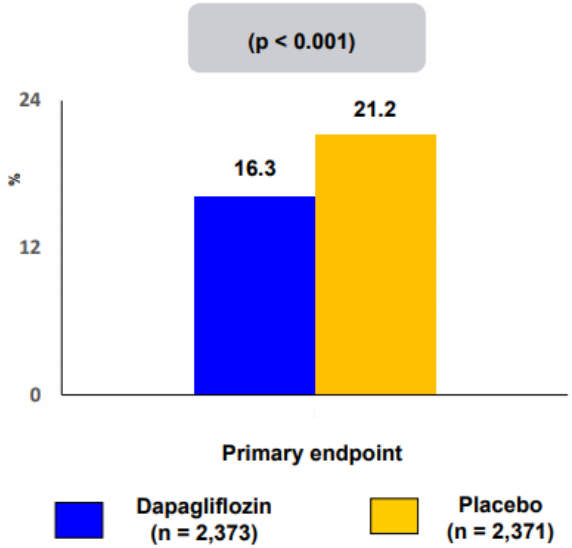
# What's New in HF in 2019

## DAPA-HF

*#ESC19*

AMERICAN COLLEGE of CARDIOLOGY

**Trial Description:** Patients with heart failure with reduced ejection fraction (irrespective of diabetes status) were randomized to dapagliflozin 10 mg daily vs. placebo.




**RESULTS**

- Primary efficacy endpoint: cardiovascular death, hospitalization for heart failure, or urgent heart failure visit occurred in 16.3% of the dapagliflozin group compared with 21.2% of the placebo group ($p < 0.001$)
- Cardiovascular death: 9.6% with dapagliflozin vs. 11.5% with placebo
- Hospitalization for heart failure: 9.7% with dapagliflozin vs. 13.4% with placebo

**CONCLUSIONS**

- Among patients with symptomatic heart failure due to reduced left ventricular ejection fraction, dapagliflozin was beneficial
- Dapagliflozin vs. placebo was associated with a reduction in cardiovascular deaths and heart failure events

**McMurray JJ, et al. N Engl J Med 2019;Sep 19:[Epub]**

https://www.escardio.org/The-ESC/Press-Office/Press-releases/dapagliflozin-reduces-death-and-hospitalisation-in-patients-with-heart-failure

# What's New in HF in 2019

## Dapagliflozin reduces death and hospitalisation in patients with heart failure

### DAPA-HF trial presented in a Hot Line Session today at ESC Congress 2019 together with WCC

01 Sep 2019

**Topic(s):** *Diabetes and the Heart; Heart Failure;*

**Paris, France – 1 Sept 2019:** Dapagliflozin reduces death and hospitalisation in patients with heart failure and reduced ejection fraction with and without diabetes. The late breaking results of the DAPA-HF trial are presented in a Hot Line Session today at ESC Congress 2019 together with the World Congress of Cardiology(1).

He concluded: "The trial shows that dapagliflozin reduces death and hospitalisation, and improves health-related quality of life, in patients with heart failure and reduced ejection fraction, with and without diabetes. The clinical implications are potentially huge – few drugs achieve these results in heart failure and dapagliflozin does even when added to excellent standard therapy."

https://www.escardio.org/The-ESC/Press-Office/Press-releases/dapagliflozin-reduces-death-and-hospitalisation-in-patients-with-heart-failure

# What's Coming in 2020

The **EMPEROR (EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure)** chronic heart failure studies are two phase III, randomized, double-blind trials investigating once-daily empagliflozin compared with placebo in adults with chronic heart failure with preserved or reduced ejection fraction*, both with and without diabetes, who are receiving current standard of care:

**EMPEROR-Preserved [NCT03057951]:** will investigate the safety and efficacy of empagliflozin in patients with chronic heart failure with **preserved ejection fraction** (HFpEF).

- Primary endpoint: time to first event of adjudicated cardiovascular death or adjudicated hospitalization for heart failure (HHF) [Time Frame: up to 38 months]
- Anticipated number of patients: approx. 5,250
- Estimated completion: 2020

**EMPEROR-Reduced [NCT03057977]:** will investigate the safety and efficacy of empagliflozin in patients with chronic heart failure with **reduced ejection fraction** (HFrEF).

- Primary endpoint: time to first event of adjudicated cardiovascular death or adjudicated HHF [Time Frame: up to 38 months]
- Anticipated number of patients: approx. 3,600
- Estimated completion: 2020

https://www.boehringer-ingelheim.us/press-release/us-fda-grants-fast-track-designation-empagliflozin-treatment-chronic-heart-failure

# Thank You!

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