Ohio-ACC Spring Summit 2014:
7th Annual CCA Cardiovascular Update &
51st Annual Carl J. Wiggers
Memorial Lecture

Heart Failure 2014: It's No Longer about Failure

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- Consultant/speaker/honoraria: none
- Editorial Boards: American Heart Journal, American Journal of Cardiology (*associate editor);* Circulation; Circulation-Heart Failure; Circulation- Quality Outcomes; Congestive Heart Failure
- Guideline writing committees: Chair, ACC/AHA, chronic HF; member, hypertrophic cardiomyopathy; member, ACC/AHA Guideline Taskforce, chair, methodology subcommittee
- Federal appointments: FDA: Chair, Cardiovascular Device Panel; ad hoc consultant; NIH CICS study section; advisory committee to the Director; AHRQ- adhoc study section chair; NHLBI- consultant; PCORI- committee member
- Volunteer Appointments: American Heart Association- President, American Heart Association, 2009-2010; American College of Cardiology, Founder- CREDO

2013 ACCF/AHA Guideline for the Management of Heart Failure

(" What's new in the 2013 ACCF/AHA Heart Failure Guidelines")

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

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*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply; see Appendix 1 for recusal information. †ACCF/AHA Representative. ‡ACCF/AHA Task Force on Practice Guidelines Liaison. §American College of Physicians Representative. ‖American College of Chest Physicians Representative. ¶International Society for Heart and Lung Transplantation Representative. #ACCF/AHA Task Force on Performance Measures Liaison. **American Academy of Family Physicians Representative. ††Heart Rhythm Society Representative.

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Definition of Heart Failure

Classification	Ejection Fraction	Description
I. Heart Failure with Reduced Ejection Fraction (HF*r*EF)	≤40%	Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HF*r*EF and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart Failure with Preserved Ejection Fraction (HF*p*EF)	≥50%	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, Borderline	41% to 49%	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HF*p*EF.
b. HF*p*EF, Improved	>40%	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

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From Risk Factors to Heart Failure: The Cardiovascular Continuum

Risk factors
•Hyperlipidemia
•Hypertension
•Diabetes
•Insulin resistance

→ Atherosclerosis LVH → CAD → Myocardial ischemia → Coronary thrombosis → Myocardial infarction → Arrhythmia → Sudden death

Myocardial infarction → Loss of muscle → Remodeling *(due to neurohormonal activation)* → Ventricular dilation → Heart failure → Death

Ventricular dilation → Sudden death; Ventricular dilation → Death

Stage A

Stage B

Stage C

Stage D

Adapted from Dzau and Braunwald. Am Heart J. 1991;131:1244-1263.

Stages, Phenotypes and Treatment of HF

At Risk for Heart Failure

Heart Failure

STAGE A
At high risk for HF but without structural heart disease or symptoms of HF

e.g., Patients with:
- HTN
- Atherosclerotic disease
- DM
- Obesity
- Metabolic syndrome

or

Patients
- Using cardiotoxins
- With family history of cardiomyopathy

→ Structural heart disease →

STAGE B
Structural heart disease but without signs or symptoms of HF

e.g., Patients with:
- Previous MI
- LV remodeling including LVH and low EF
- Asymptomatic valvular disease

→ Development of symptoms of HF →

STAGE C
Structural heart disease with prior or current symptoms of HF

e.g., Patients with:
- Known structural heart disease and
- HF signs and symptoms

→ Refractory symptoms of HF at rest, despite GDMT →

STAGE D
Refractory HF

e.g., Patients with:
- Marked HF symptoms at rest
- Recurrent hospitalizations despite GDMT

THERAPY (Stage A)

Goals
- Heart healthy lifestyle
- Prevent vascular, coronary disease
- Prevent LV structural abnormalities

Drugs
- ACEI or ARB in appropriate patients for vascular disease or DM
- Statins as appropriate

THERAPY (Stage B)

Goals
- Prevent HF symptoms
- Prevent further cardiac remodeling

Drugs
- ACEI or ARB as appropriate
- Beta blockers as appropriate

In selected patients
- ICD
- Revascularization or valvular surgery as appropriate

HF*p*EF

THERAPY

Goals
- Control symptoms
- Improve HRQOL
- Prevent hospitalization
- Prevent mortality

Strategies
- Identification of comorbidities

Treatment
- Diuresis to relieve symptoms of congestion
- Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
- Revascularization or valvular surgery as appropriate

HF*r*EF

THERAPY

Goals
- Control symptoms
- Patient education
- Prevent hospitalization
- Prevent mortality

Drugs for routine use
- Diuretics for fluid retention
- ACEI or ARB
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- Aldosterone antagonists

Drugs for use in selected patients
- Hydralazine/isosorbide dinitrate
- ACEI and ARB
- Digoxin

In selected patients
- CRT
- ICD
- Revascularization or valvular surgery as appropriate

THERAPY (Stage D)

Goals
- Control symptoms
- Improve HRQOL
- Reduce hospital readmissions
- Establish patient's end-of-life goals

Options
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

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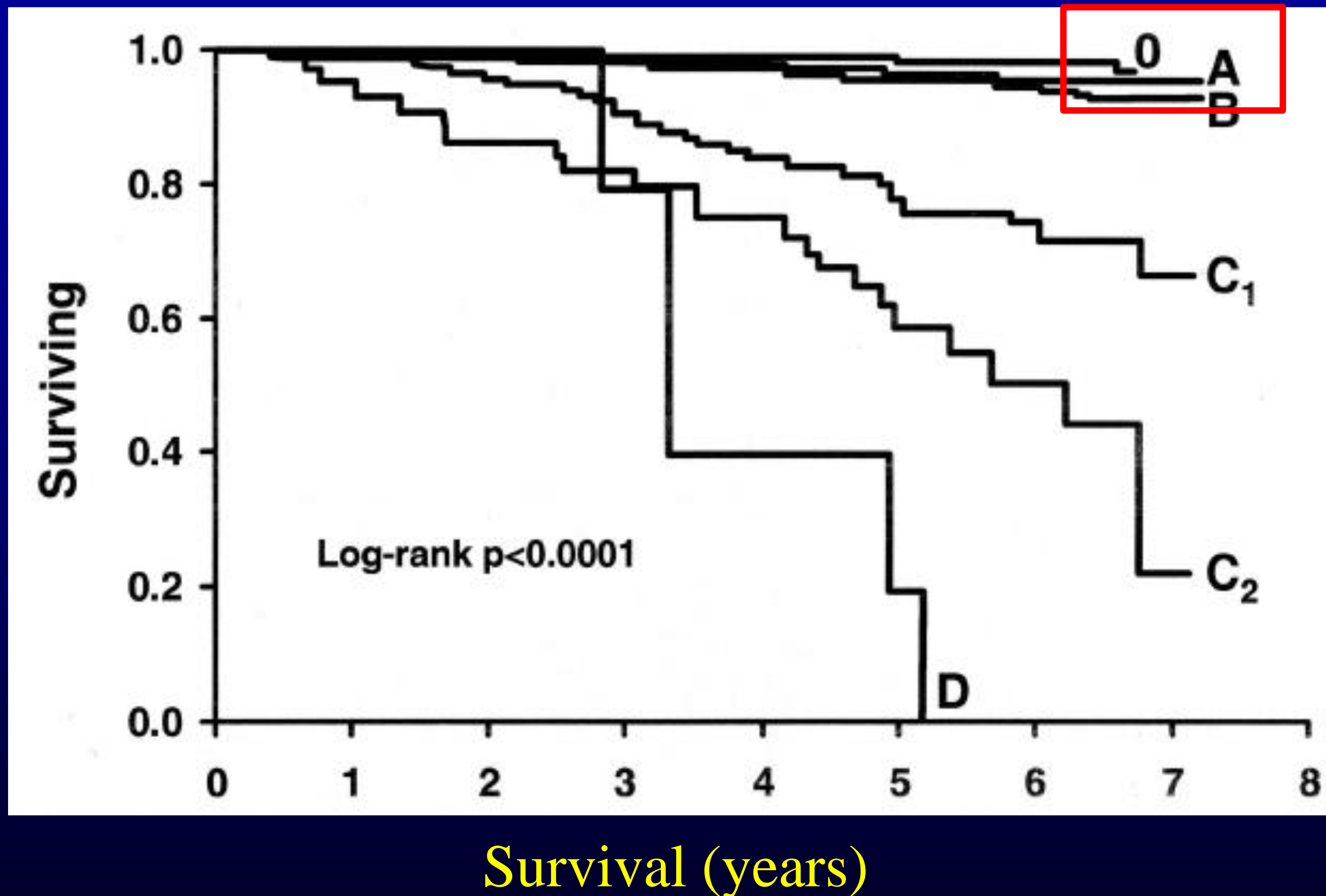
Prevalence and prognostic significance of HF Stages

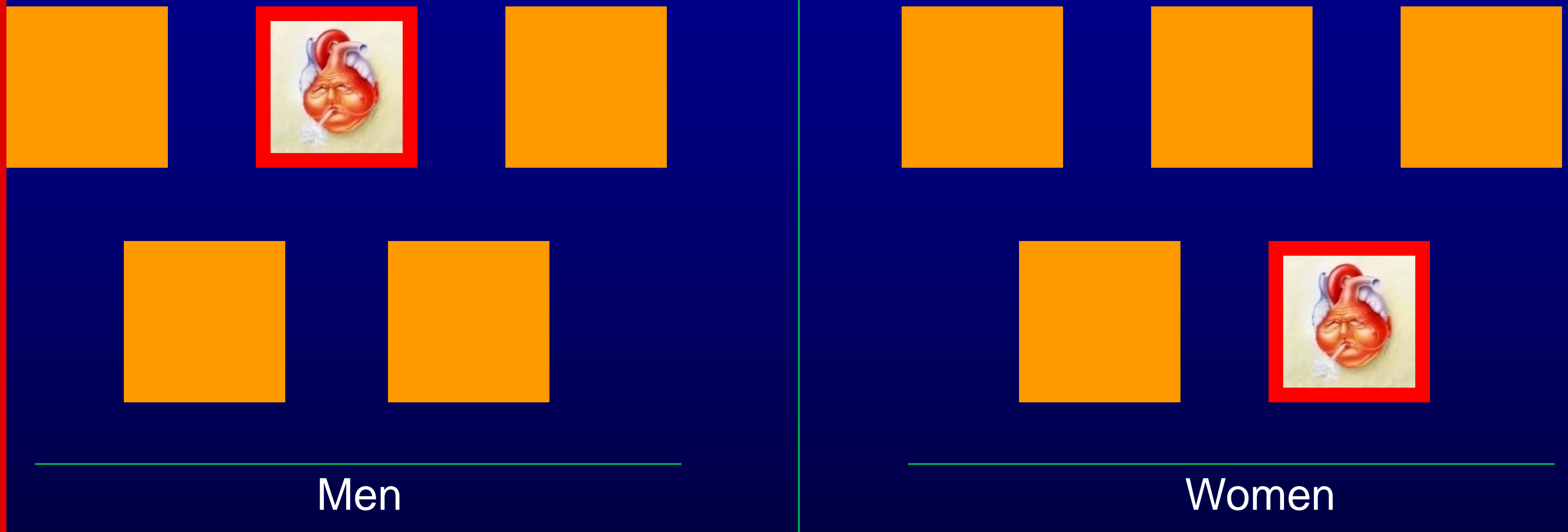


Survival (years)

Ammar et al. *Circulation* 2007; 115:1563

The prevention of heart failure?

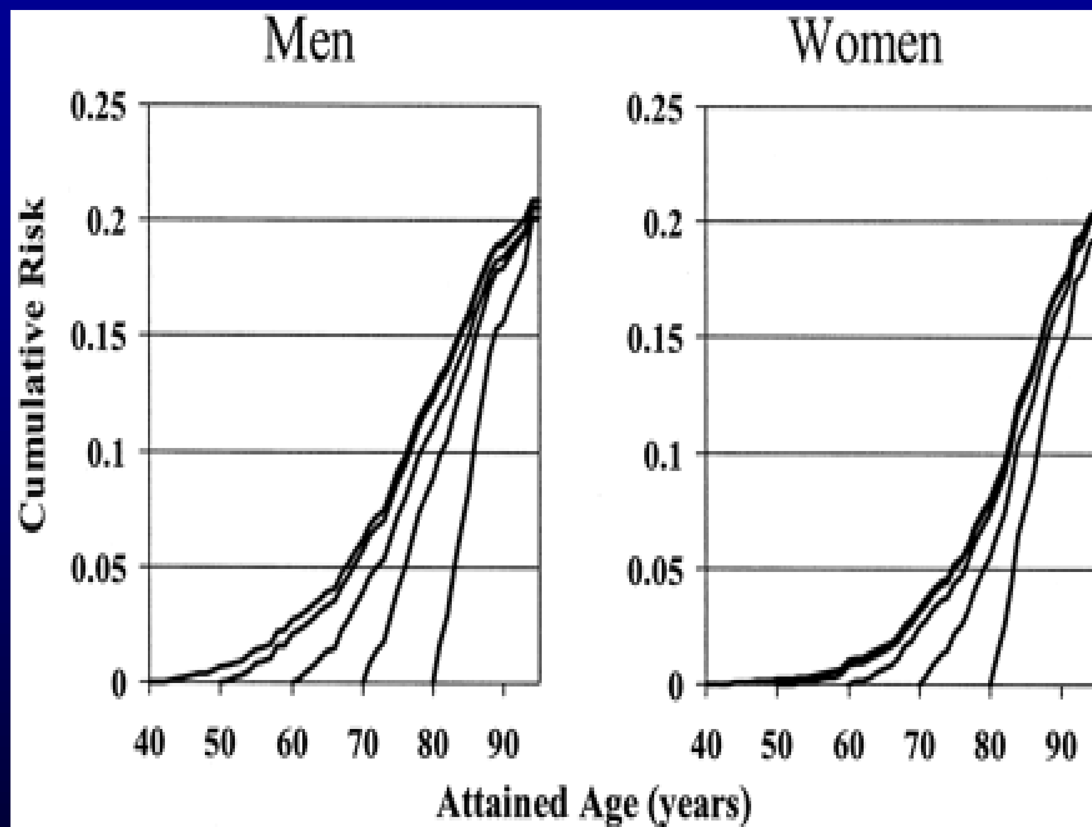
Lifetime Risk for Developing Heart Failure



- At age 40 years, the lifetime risk for HF was 21.0% (95% CI, 18.7%-23.2%) for men and 20.3% (95% CI, 18.2%-22.5%) for women

Lloyd-Jones, et al. *Circulation.* 2002;106:3068-3072.

Comparison of short-term vs lifetime cumulative risks of CHF for men and women at selected index ages



ONE IN FIVE INDIVIDUALS WILL DEVELOP HF

FRAMINGHAM Donald M. Lloyd-Jones et al Circulation 2002;106:3068

PREVENTING HEART FAILURE?

IS IT POSSIBLE?

- Diabetes
- Where we are
- Where we need to be

DIABETES AND HEART FAILURE

- **Risk of Developing Heart Failure in Diabetes (Framingham)**
- **Fourfold increase in young diabetic males (≤ 65 year old)**
- **Eightfold increase in young diabetic females (≤ 65 years old)**

- **Percentage of patients with diabetes in heart failure trials**
- **23% in Consensus**
- **25% in SOLVD**
- **20% in ATLAS**
- **24% in COMET**

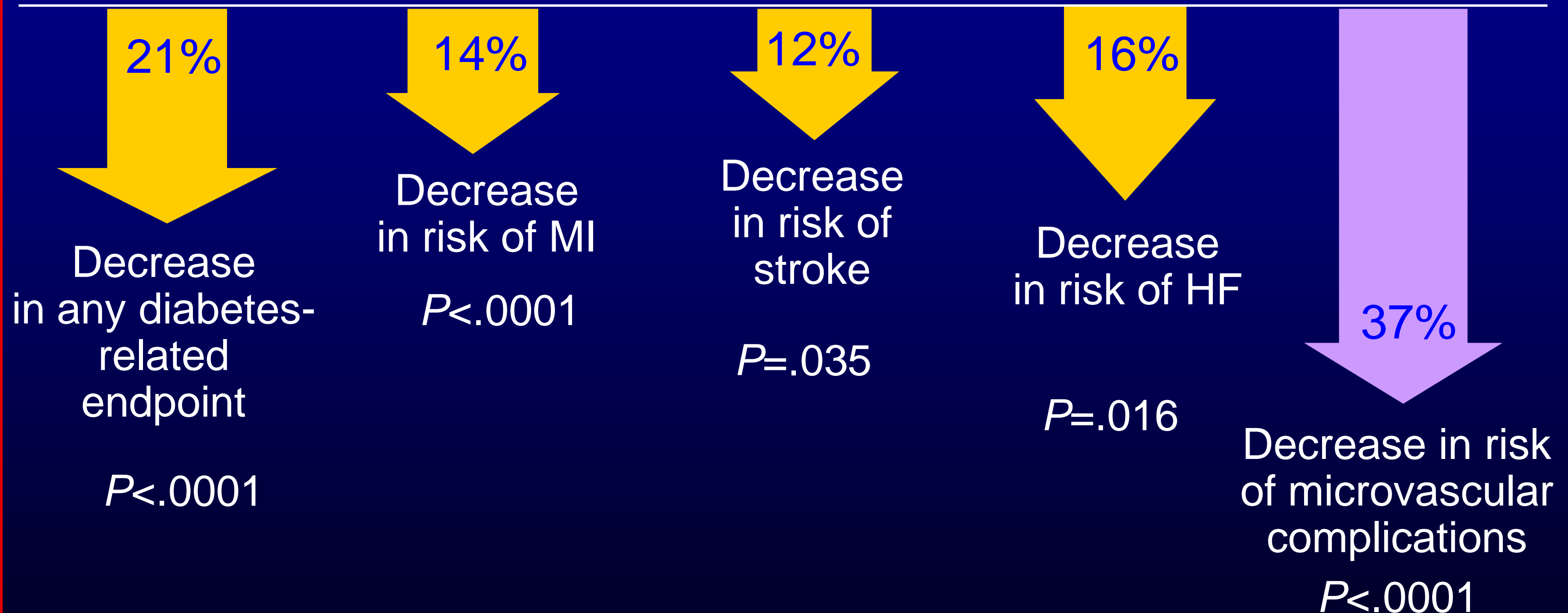
UKPDS - Hypertension Study
Benefits of 144/82 vs 154/87

- Tight BP control, with either a beta-blocker or an ACE inhibitor, in Type 2 Diabetics decreases:
  - Death related to diabetes by - 32%
  - Stroke by - 44%
  - Microvascular disease by - 37%
  - Heart failure by - 56%
  - Progression of retinopathy by - 34%
  - Deterioration of visual acuity by - 47%
  - BP target < 130/80 for diabetics and in chronic renal disease JNC-VII

BMJ 1998;317:703-713 NIH publication #4 5230

The Need for Tight Glycemic Control

UKPDS 35,
every 1% drop in HbA_{1c} was associated with:



United Kingdom Prospective Diabetes Study (UKPDS) 35 was a prospective observational study of 4,585 DM patients with a mean age of 53 years. Median follow-up time (duration of diabetes) was 10 years.
HF=heart failure; MI=myocardial infarction.

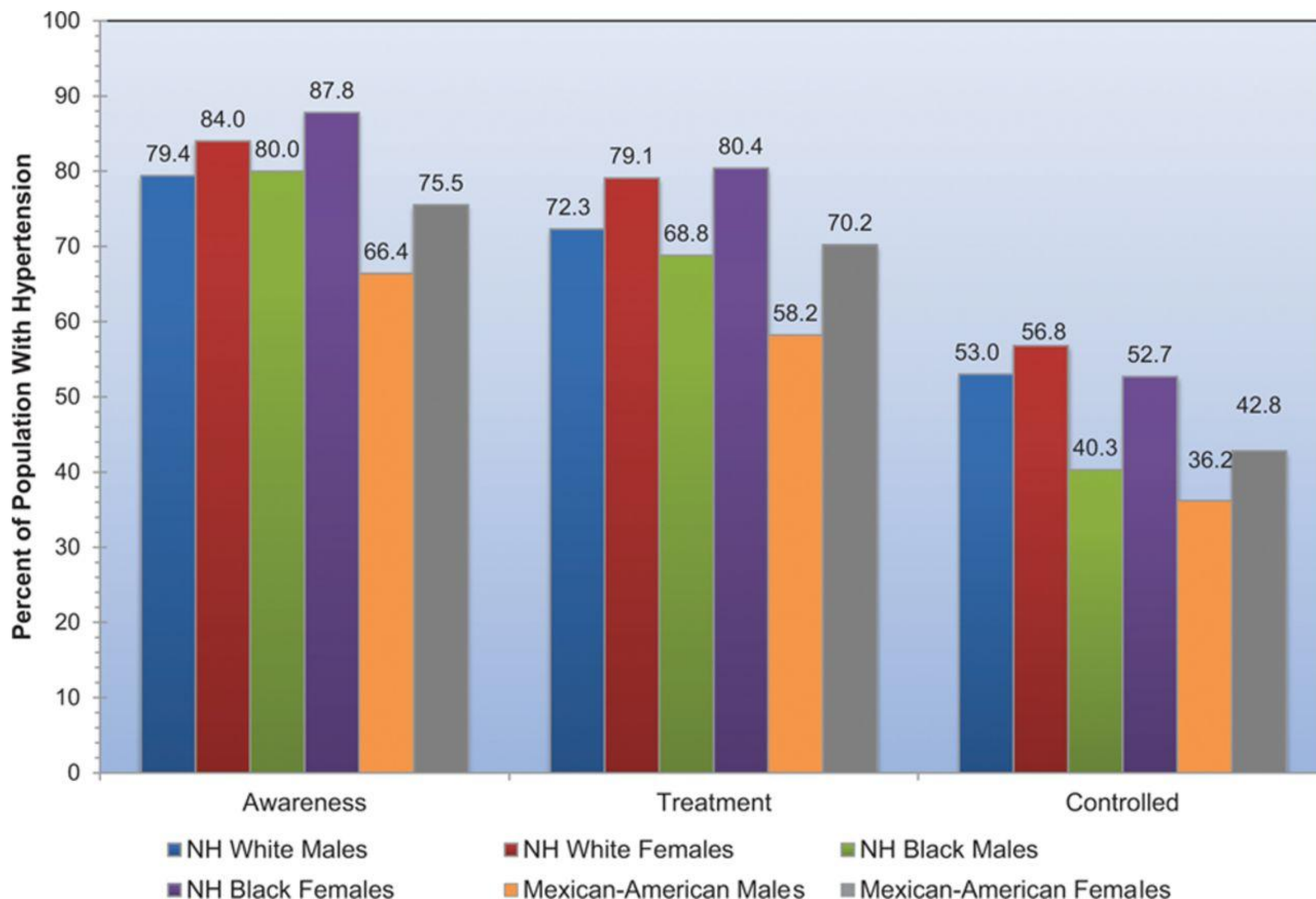
Stratton IM, et al. *BMJ*. 2000;321:405-12.

PREVENTING HEART FAILURE?

IS IT POSSIBLE?

- Hypertension
- Where we are
- Where we need to be

Extent of awareness, treatment, and control of high blood pressure by race/ethnicity and sex (National Health and Nutrition Examination Survey: 2007–2010).



Go A et al. Circulation 2014;129:e28-e292

American Heart Association

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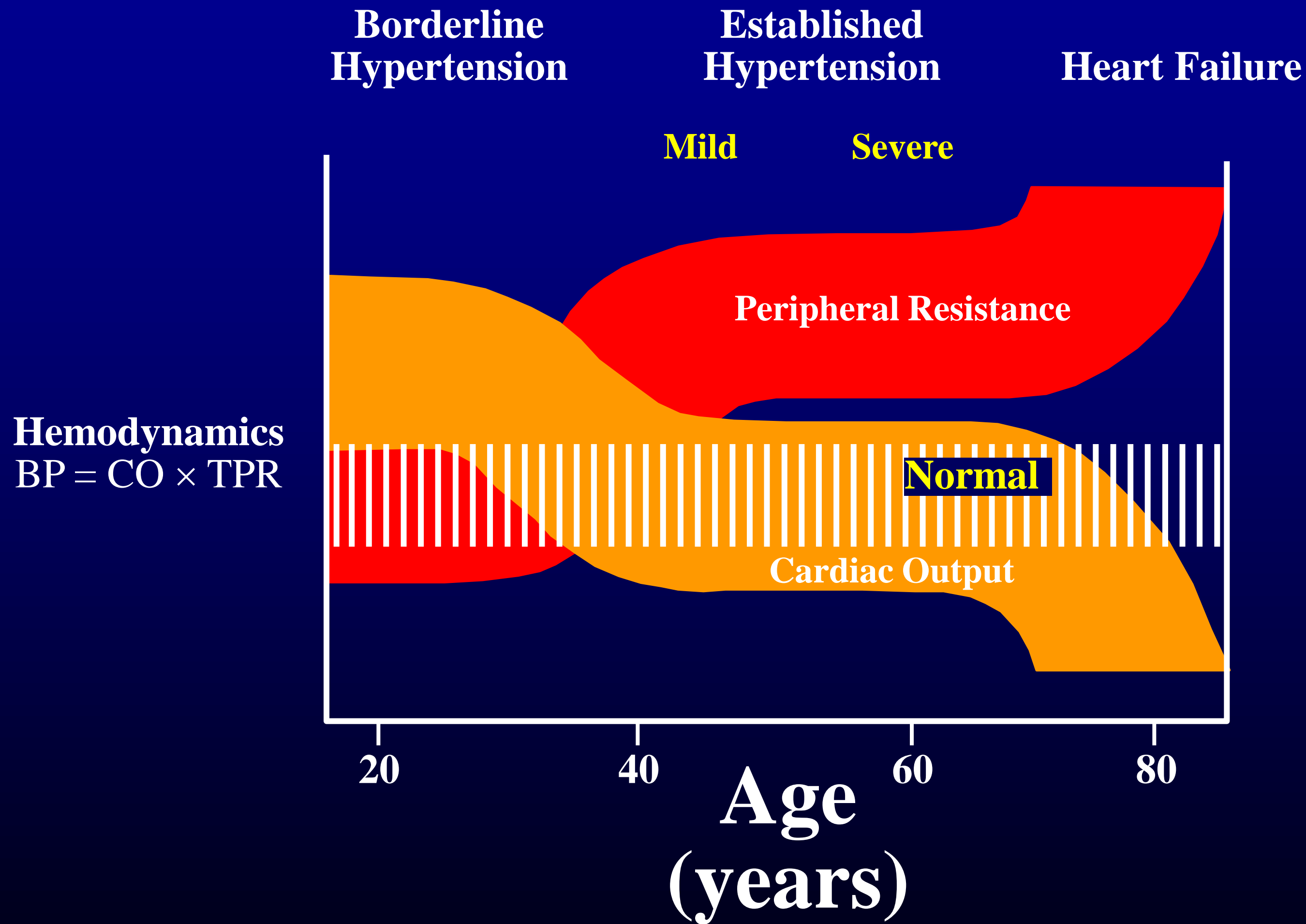
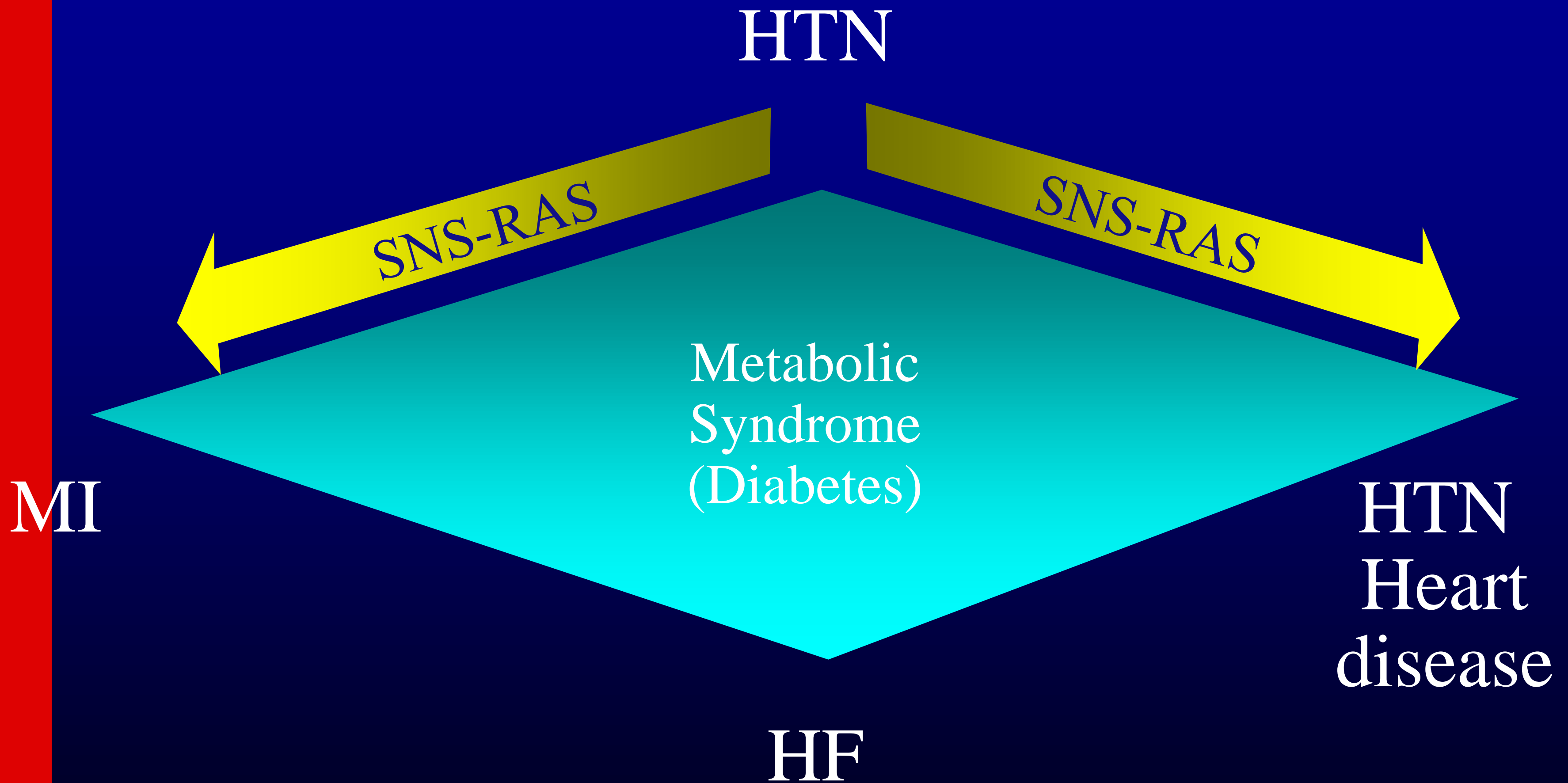
Change in Hemodynamic Profile With Age



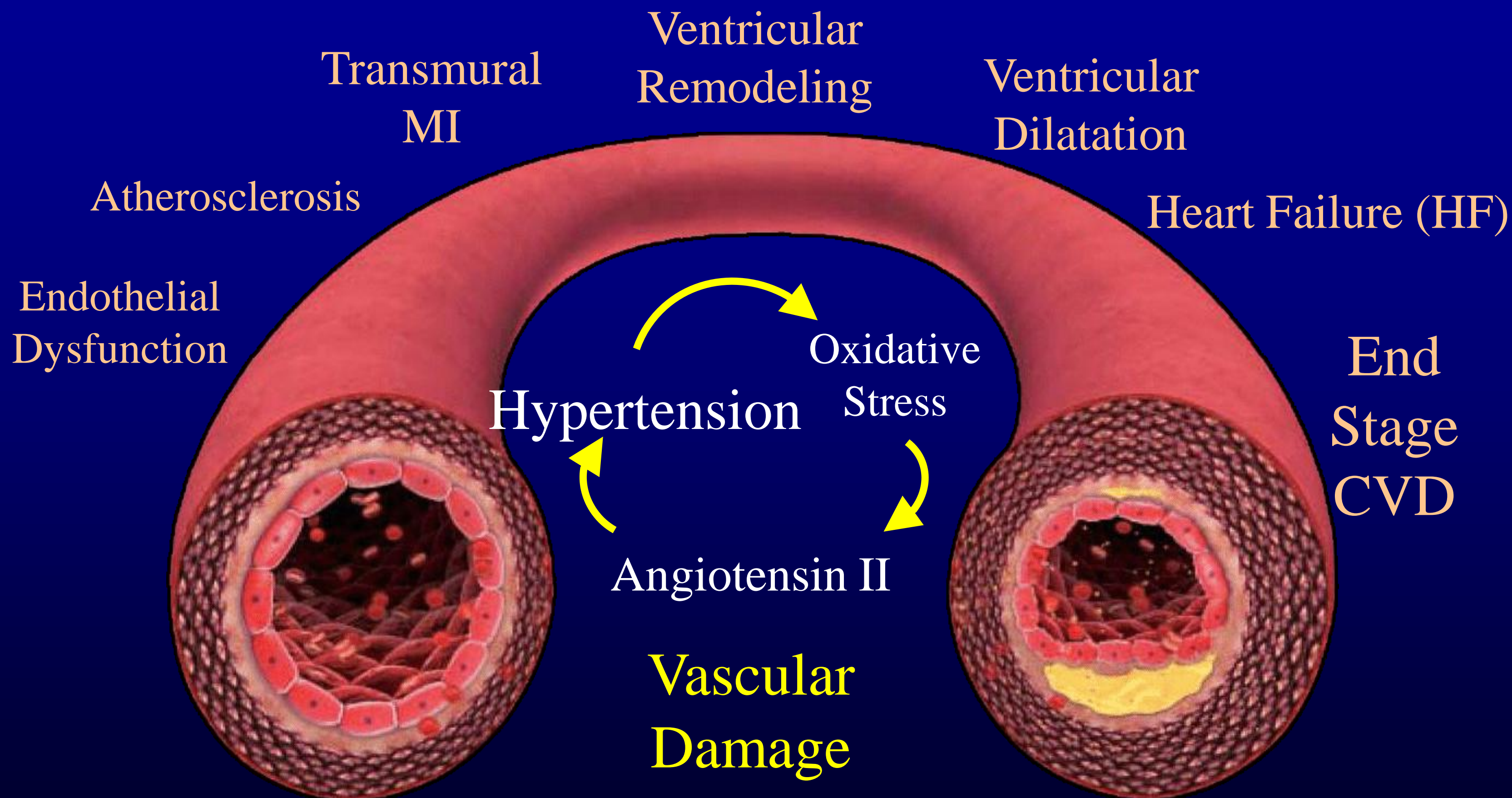
Messerli FH. *J Clin Pharmacol*. 1981;21:517-528.

Evolution to Heart Failure



Pharmacotherapy. 2000;20:495.

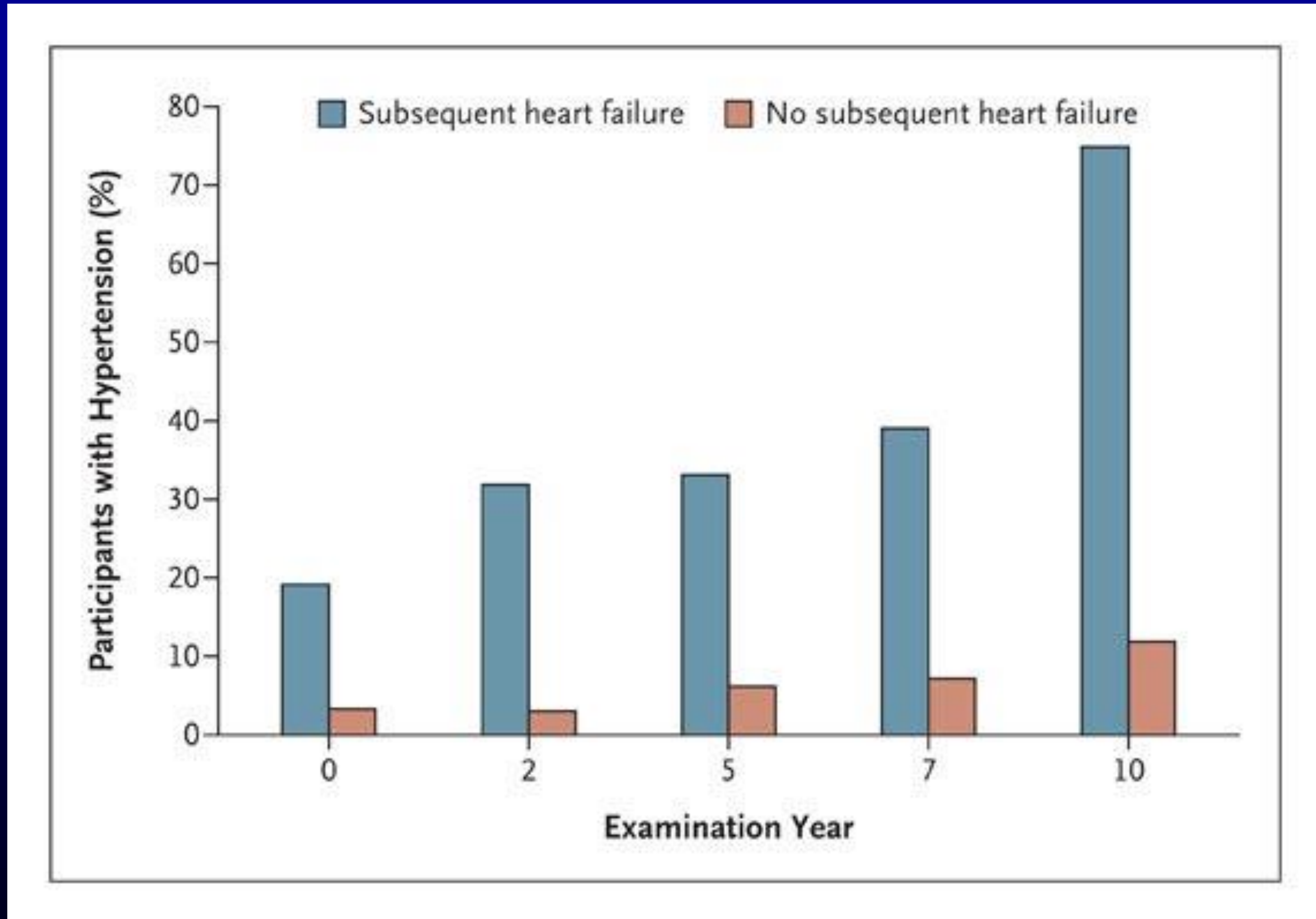
Hypertension Is Associated With Vascular Damage Along the Entire CV Continuum



Adapted from Dzau V et al. *Am Heart J*. 1991;121:1244–1263.

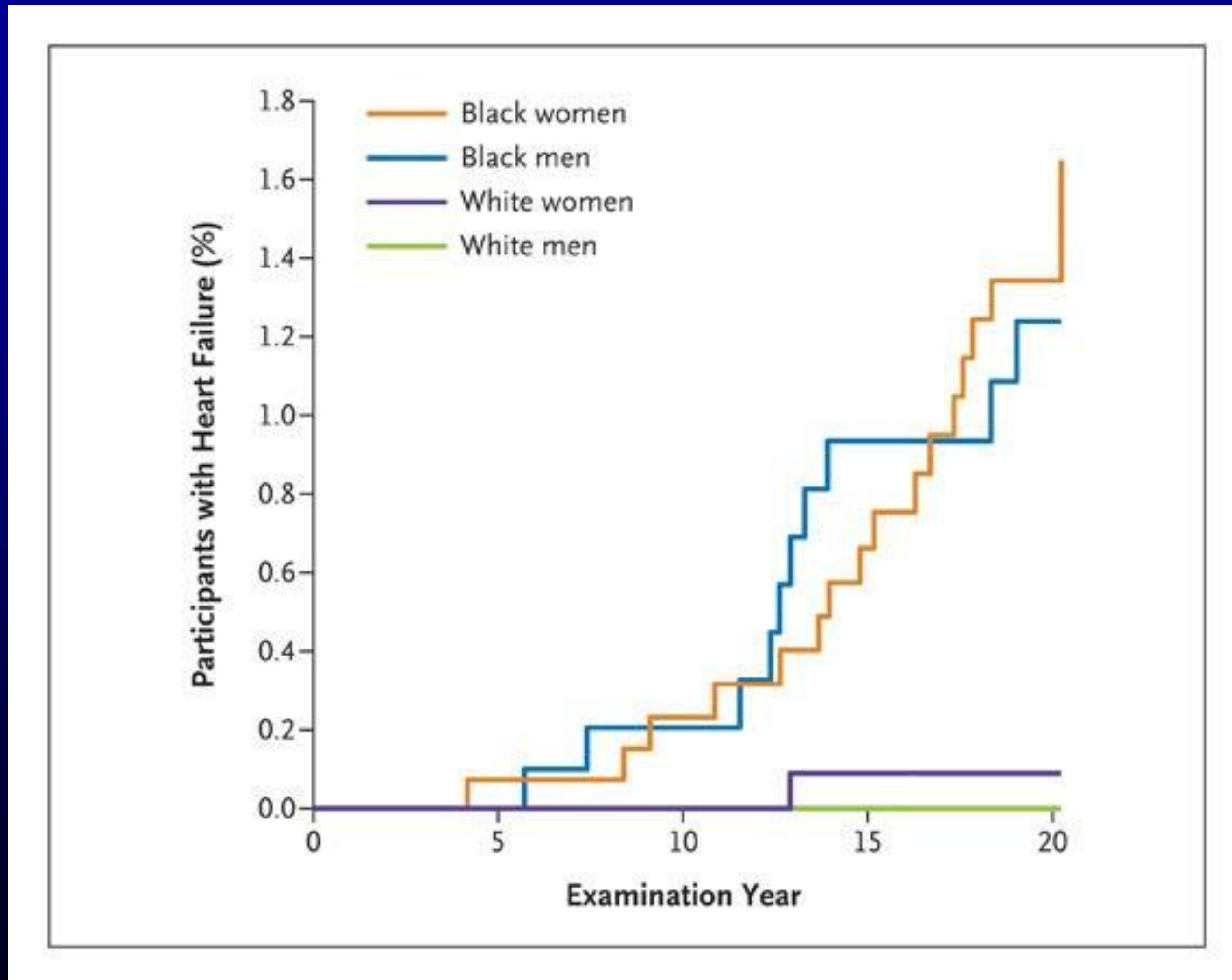
HF in African Americans- *are there fundamental differences?*

Hypertension as a risk factor for HF in AAs



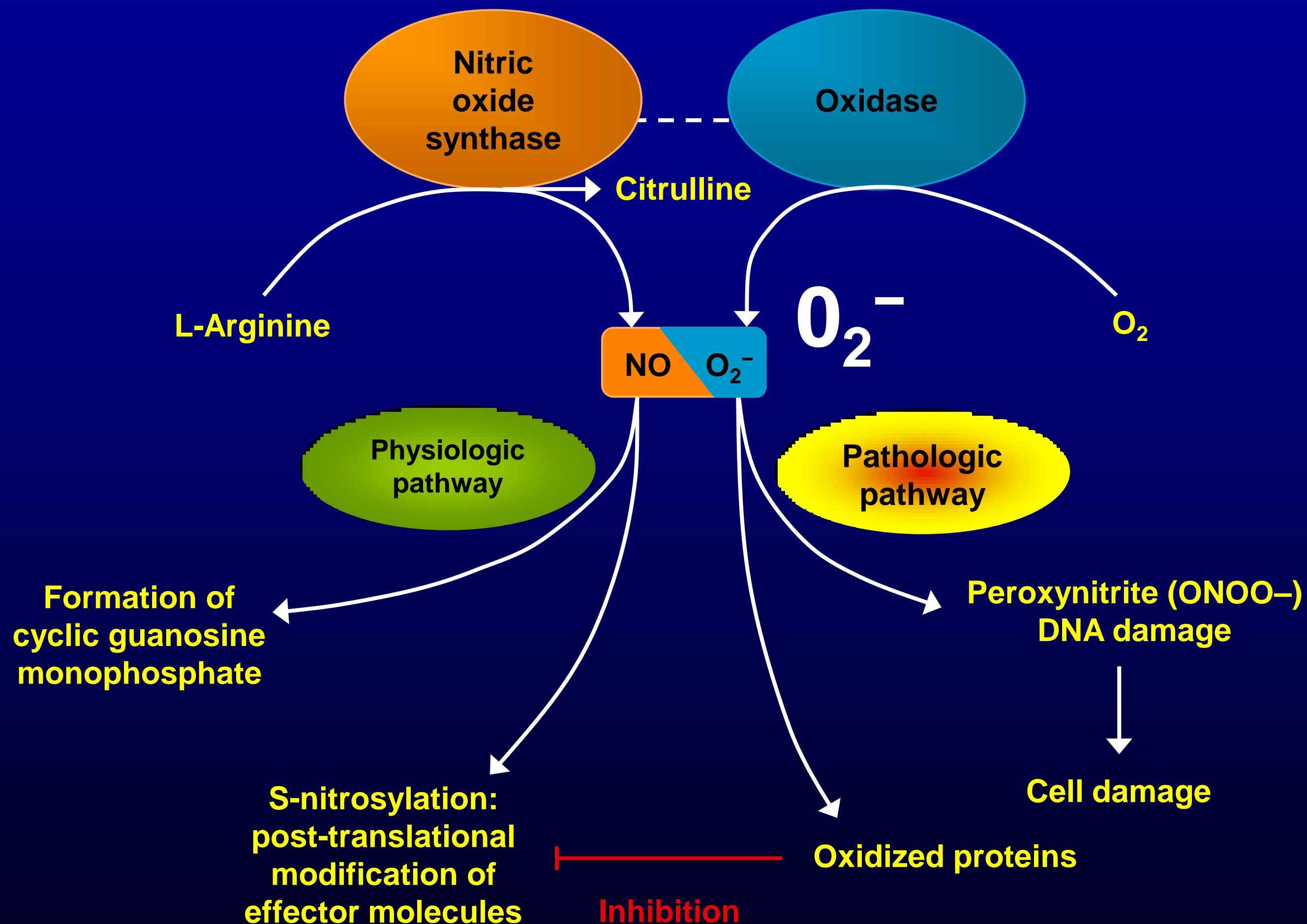
Bibbins-Domingo et al. New England Journal of Medicine. 360(12):1179-1190

Incidence of heart failure in young AAs



Bibbins-Domingo et al. New England Journal of Medicine. 360(12):1179-1190

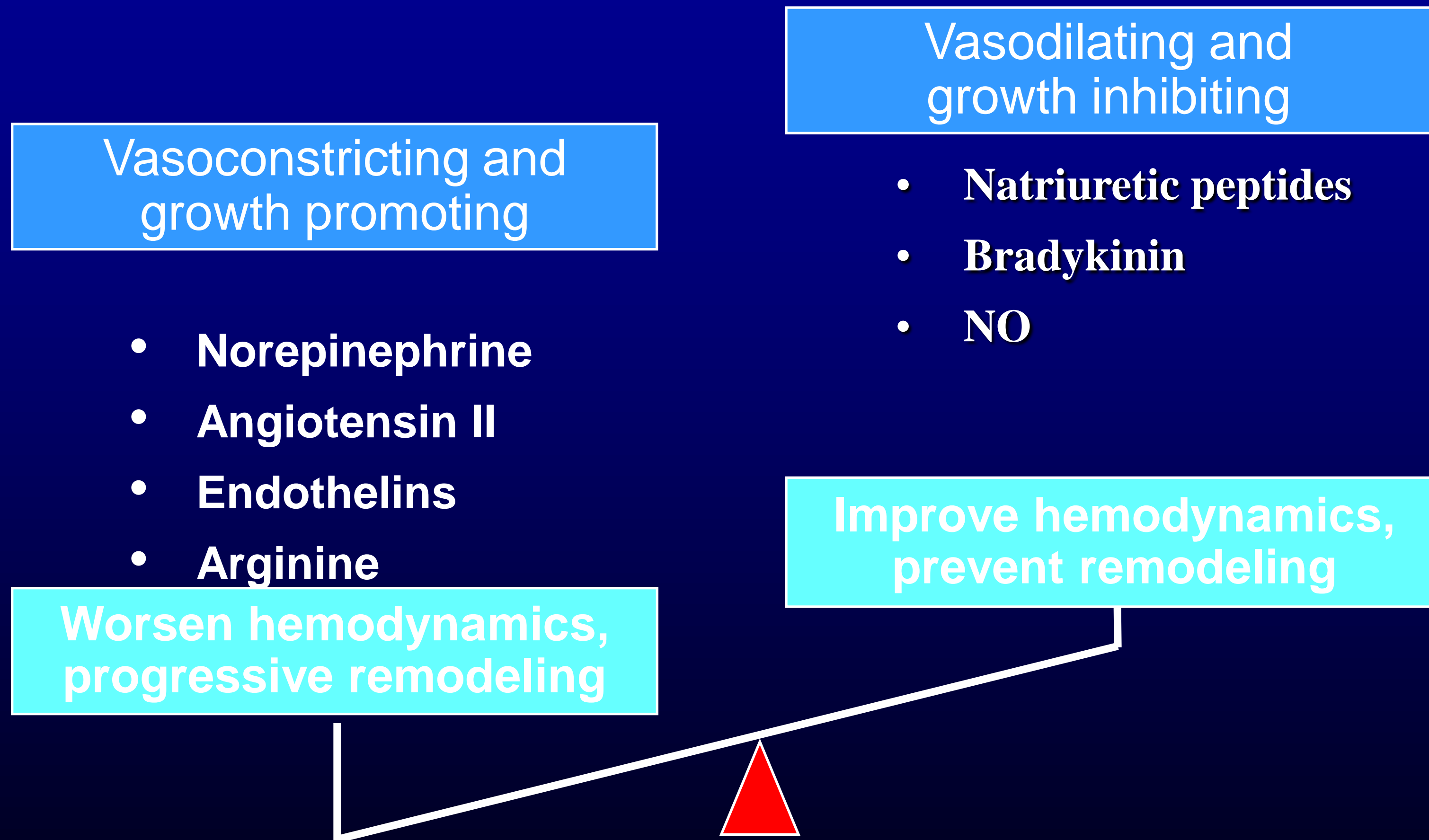
Consequences of Nitric Oxide and Super Oxide Balance Disruption in Heart Failure Patients



Hare JM. *N Engl J Med.* 2004;351:2112-2114.

The NO Paradigm in HF

A System Out of Balance in AAs?



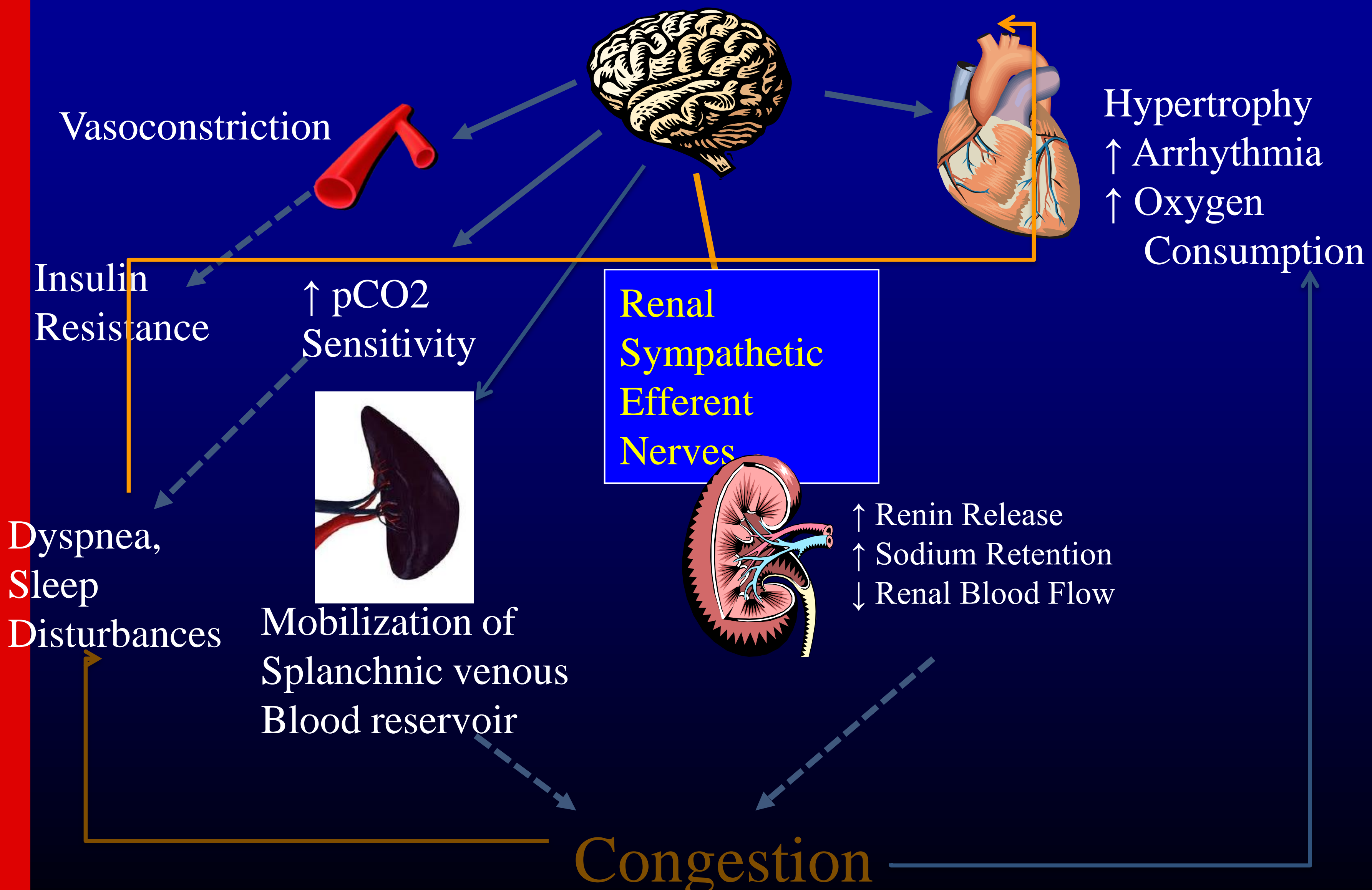
Yancy CW. Heart Failure in African Americans: The State of the Art. Presented at 8th Annual Scientific Meeting of the Heart Failure Society of America. September 12, 2004; Toronto, Canada.

PREVENTING HEART FAILURE?

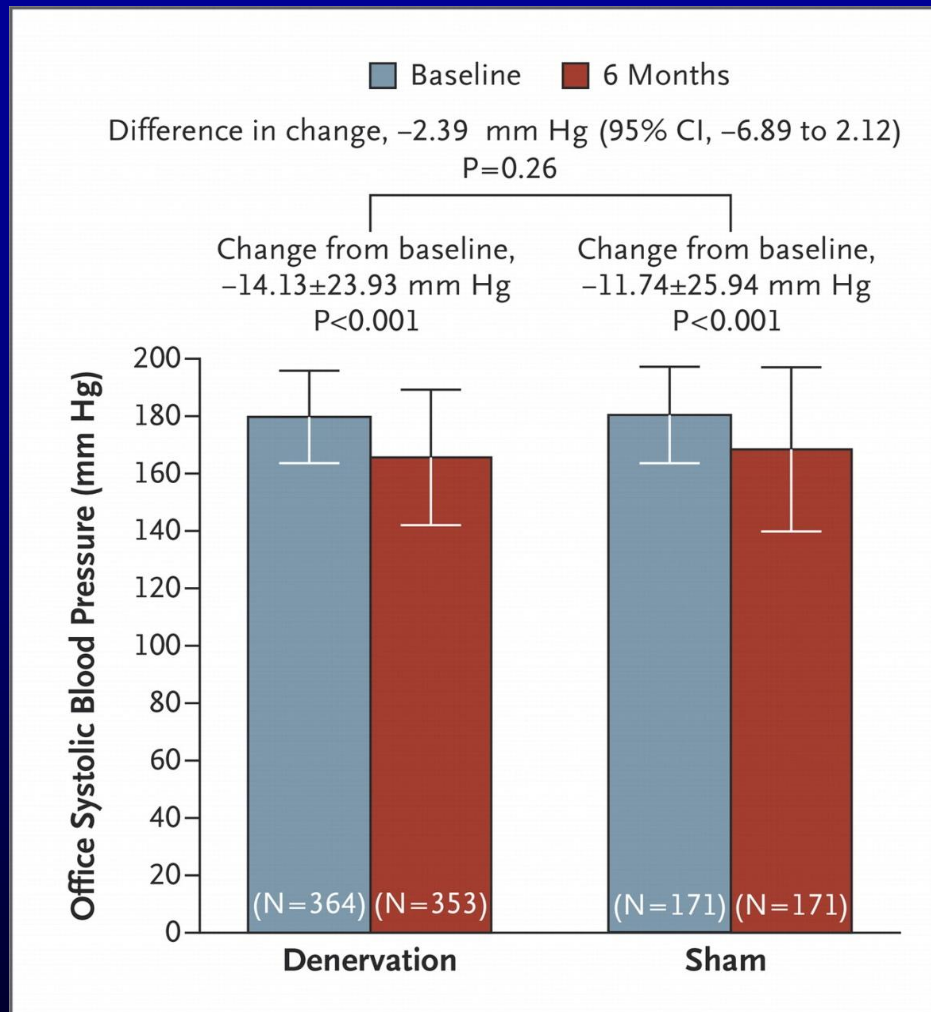
IS IT POSSIBLE?

- Hypertension
- Where we are
- Where we need to be

Consequences of Chronic Elevated Central Sympathetic Drive



Primary Efficacy End Point.

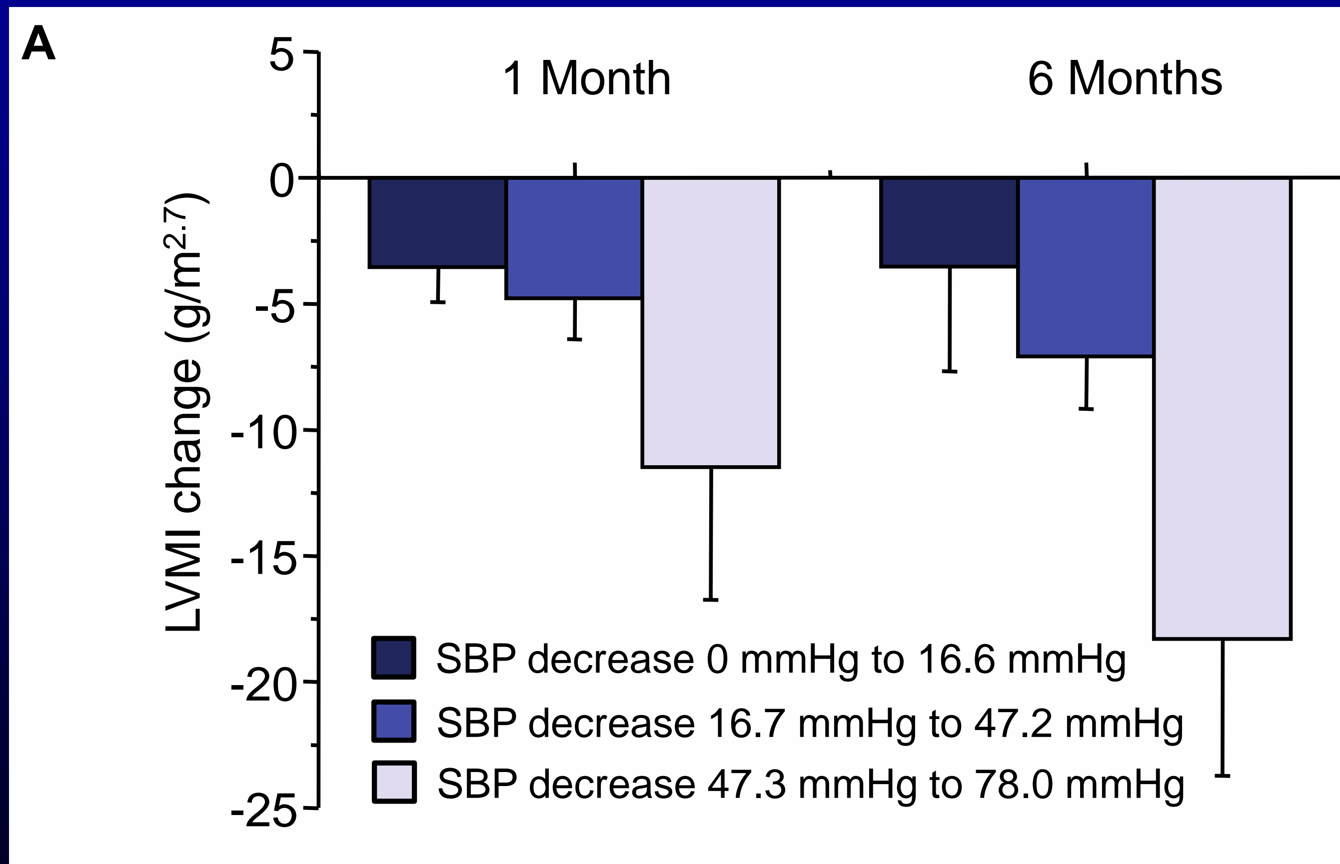


Bhatt DL et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1402670

The NEW ENGLAND JOURNAL of MEDICINE

Regression of LVH and Improvement of Diastolic Function Depending on BP Reduction Achieved by RD

Regression of LV mass/height$^{2.7}$



J Am Coll Cardiol 2012;59: 901-9

Stage A

Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF.

Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided.

Stages, Phenotypes and Treatment of HF

At Risk for Heart Failure | **Heart Failure**

STAGE A
At high risk for HF but without structural heart disease or symptoms of HF

e.g., Patients with:
- HTN
- Atherosclerotic disease
- DM
- Obesity
- Metabolic syndrome

or

Patients
- Using cardiotoxins
- With family history of cardiomyopathy

→ Structural heart disease →

THERAPY

Goals
- Heart healthy lifestyle
- Prevent vascular, coronary disease
- Prevent LV structural abnormalities

Drugs
- ACEI or ARB in appropriate patients for vascular disease or DM
- Statins as appropriate

STAGE B
Structural heart disease but without signs or symptoms of HF

e.g., Patients with:
- Previous MI
- LV remodeling including LVH and low EF
- Asymptomatic valvular disease

→ Development of symptoms of HF →

THERAPY

Goals
- Prevent HF symptoms
- Prevent further cardiac remodeling

Drugs
- ACEI or ARB as appropriate
- Beta blockers as appropriate

In selected patients
- ICD
- Revascularization or valvular surgery as appropriate

STAGE C
Structural heart disease with prior or current symptoms of HF

e.g., Patients with:
- Known structural heart disease and
- HF signs and symptoms

→ Refractory symptoms of HF at rest, despite GDMT →

HF*p*EF

THERAPY

Goals
- Control symptoms
- Improve HRQOL
- Prevent hospitalization
- Prevent mortality

Strategies
- Identification of comorbidities

Treatment
- Diuresis to relieve symptoms of congestion
- Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
- Revascularization or valvular surgery as appropriate

HF*r*EF

THERAPY

Goals
- Control symptoms
- Patient education
- Prevent hospitalization
- Prevent mortality

Drugs for routine use
- Diuretics for fluid retention
- ACEI or ARB
- Beta blockers
- Aldosterone antagonists

Drugs for use in selected patients
- Hydralazine/isosorbide dinitrate
- ACEI and ARB
- Digoxin

In selected patients
- CRT
- ICD
- Revascularization or valvular surgery as appropriate

STAGE D
Refractory HF

e.g., Patients with:
- Marked HF symptoms at rest
- Recurrent hospitalizations despite GDMT

THERAPY

Goals
- Control symptoms
- Improve HRQOL
- Reduce hospital readmissions
- Establish patient's end-of-life goals

Options
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

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Treatment of Stages A to D

Stage B

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Recommendations for Treatment of Stage B HF

Recommendations	COR	LOE
In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF	I	A
In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF	I	B
In patients with MI, statins should be used to prevent HF	I	A
Blood pressure should be controlled to prevent symptomatic HF	I	A
ACE inhibitors should be used in all patients with a reduced EF to prevent HF	I	A
Beta blockers should be used in all patients with a reduced EF to prevent HF	I	C
An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT	IIa	B
Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF	III: Harm	C

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STAGE B
Structural heart disease but without signs or symptoms of HF

e.g., Patients with:
- Previous MI
- LV remodeling including LVH and low EF
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→ Development of symptoms of HF

THERAPY

Goals
- Prevent HF symptoms
- Prevent further cardiac remodeling

Drugs
- ACEI or ARB as appropriate
- Beta blockers as appropriate

In selected patients
- ICD
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STAGE C
Structural heart disease with prior or current symptoms of HF

e.g., Patients with:
- Known structural heart disease and
- HF signs and symptoms

→ Refractory symptoms of HF at rest, despite GDMT

HF*p*EF

THERAPY

Goals
- Control symptoms
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Strategies
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Treatment
- Diuresis to relieve symptoms of congestion
- Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
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HF*r*EF

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Drugs for routine use
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STAGE D
Refractory HF

e.g., Patients with:
- Marked HF symptoms at rest
- Recurrent hospitalizations despite GDMT

THERAPY

Goals
- Control symptoms
- Improve HRQOL
- Reduce hospital readmissions
- Establish patient's end-of-life goals

Options
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

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Treatment for Stage C HF*p*EF

TOPCAT - Results

- 3,445 patients were randomized, 1,722 to spironolactone and to 1,723 to placebo.
- Baseline characteristics were similar between the two arms.
- The baseline EF was 56%
- 52% were female
- 2/3 of the patients had New York Heart Association (NYHA) class II symptoms.
- Hypertension was present in 92% of patients. Coronary artery disease was noted in 59% and atrial fibrillation in 35%.
- Baseline K was 4.3 mEq/L.

The primary endpoint of CV death, chronic HF (CHF) hospitalization, or resuscitated cardiac arrest over 6 years was similar between the spironolactone and placebo arms (18.6% vs. 20.4%, hazard ratio = 0.89, 95% confidence interval 0.77-1.04, p = 0.14).

- Individual components including CV mortality (9.3% vs. 10.2%. p = 0.35) and aborted cardiac arrest (3 vs. 5 events, p = 0.48) were similar between the two arms.
- CHF hospitalizations were lower (12.0% vs. 14.2%, p = 0.042); all-hospitalizations were similar (p = 0.25).
- Hyperkalemia (18.7% vs. 9.1%, p < 0.001) and renal failure, defined as doubling of creatinine >2 upper limit of normal were both significantly higher in the spironolactone arm.

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Treatment of HF*p*EF

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

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American Heart Association®

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- Beta blockers as appropriate

In selected patients
- ICD
- Revascularization or valvular surgery as appropriate

Heart Failure

STAGE C
Structural heart disease with prior or current symptoms of HF

e.g., Patients with:
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HF*p*EF

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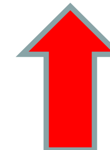

STAGE D
Refractory HF

e.g., Patients with:
- Marked HF symptoms at rest
- Recurrent hospitalizations despite GDMT

THERAPY

Goals
- Control symptoms
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- Reduce hospital readmissions
- Establish patient's end-of-life goals

Options
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- Palliative care and hospice
- ICD deactivation

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Initial and Serial Evaluation of the HF Patient

Clinical Evaluation

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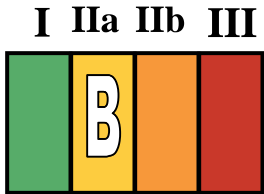
Risk Scoring



Validated multivariable risk scores can be useful to estimate subsequent risk of mortality in ambulatory or hospitalized patients with HF.

Risk Scores to Predict Outcomes in HF

Risk Score	Reference (from full-text guideline)/Link
Chronic HF	
All patients with chronic HF	
Seattle Heart Failure Model	(204) / http://SeattleHeartFailureModel.org
Heart Failure Survival Score	(200) / http://handheld.softpedia.com/get/Health/Calculator/HFSS-Calc-37354.shtml
CHARM Risk Score	(207)
CORONA Risk Score	(208)
Specific to chronic HFpEF	
I-PRESERVE Score	(202)
Acutely Decompensated HF	
ADHERE Classification and Regression Tree (CART) Model	(201)
American Heart Association Get With the Guidelines Score	(206) / http://www.heart.org/HEARTORG/HealthcareProfessional/GetWithTheGuidelinesHFStroke/GetWithTheGuidelinesHeartFailureHomePage/Get-With-The-Guidelines-Heart-Failure-Home- %20Page_UCM_306087_SubHomePage.jsp
EFFECT Risk Score	(203) / http://www.ccort.ca/Research/CHFRiskModel.aspx
ESCAPE Risk Model and Discharge Score	(215)
OPTIMIZE HF Risk-Prediction Nomogram	(216)

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Initial and Serial Evaluation of the HF Patient

Biomarkers
Ambulatory/Outpatient

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Ambulatory/Outpatient

In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty.

Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.

Predischarge BNP Is Strong Predictor of Post-Discharge Events

Death or Readmission, %

100
75
50
25
0

BNP >700 ng/L*
(n = 41, events = 38)

BNP 350-700 ng/L*
(n = 50, events = 30)

BNP <350 ng/L*
(n = 111, events = 18)

0 30 60 90 120 150 180

Follow-up, Days

p<.0001

p<.0001

1

5.1

15.2

Hazard Ratios

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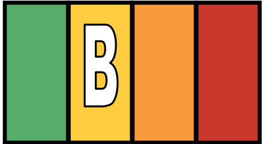
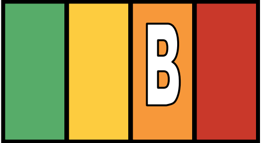
Logeart D, et al. *J Am Coll Cardiol.* 2004;43:635-641.

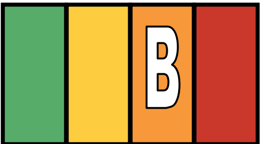
Ambulatory/Outpatient (cont.)



BNP- or NT-proBNP guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvolemic patients followed in a well-structured HF disease management program.



The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established.



Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF.

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Blocker (ARB) and β-Blocker Doses During the Study 2. Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin II Receptor

Treatment
Symptom-guided
N-terminal BNP–guided

ACE Inhibitor or ARB

β-Blocker

Percentage of Target Dose

35
30
25
20
15
10
5
0

<75
≥75

Age, y

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Pfisterer, M. et al. JAMA 2009;301:383-392

JAMA

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Changes in N-terminal B-type natriuretic peptide (NT-proBNP) during the 4-month follow-up in the Valsartan Heart Failure trial.

NT-proBNP (pg/mL)

2500
2000
1500
1000
500
0

n= 1322
n= 368
n= 180
n= 1618

0
4 months

	Mortality (%)	Hospitalization for HF (%)
High→High	25.6	26.8
Low→High	17.2	21.1
High→Low	13.6	10.1
Low→Low	8.6	6.7

Januzzi J L , Troughton R Circulation 2013;127:500-508

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Meta-analysis of 'guided therapy'

Troughton
STARBRITE
STARS-BNP
BATTLESCARRED
TIME-CHF
PRIMA

Combined

0.01 0.1 1 10

Relative Risk

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Felker et al, Am Heart Journal, 2009

Recommendations for Biomarkers in HF

Biomarker, Application	Setting	COR	LOE
Natriuretic peptides			
Diagnosis or exclusion of HF	Ambulatory, Acute	I	A
Prognosis of HF	Ambulatory, Acute	I	A
Achieve GDMT	Ambulatory	IIa	B
Guidance of acutely decompensated HF therapy	Acute	IIb	C
Biomarkers of myocardial injury			
Additive risk stratification	Acute, Ambulatory	I	A
Biomarkers of myocardial fibrosis			
Additive risk stratification	Ambulatory	IIb	B
	Acute	IIb	A

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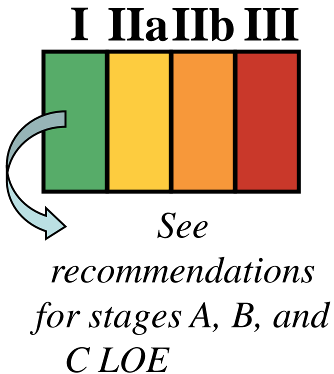
Stage C

Pharmacological Treatment for Stage C HFrEF

Pharmacological Treatment for Stage C HF*r*EF



Measures listed as Class I recommendations for patients in stages A and B are recommended where appropriate for patients in stage C. (Levels of Evidence: A, B, and C as appropriate)

GDMT as depicted in Figure 1 should be the mainstay of pharmacological therapy for HF*r*EF.

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Pharmacologic Treatment for Stage C HFrEF

HFrEF Stage C
NYHA Class I – IV
Treatment:

Class I, LOE A
ACEI or ARB **AND**
Beta Blocker

For all volume overload, NYHA class II-IV patients

For persistently symptomatic African Americans, NYHA class III-IV

For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL

Add

Add

Add

Class I, LOE C
Loop Diuretics

Class I, LOE A
Hydral-Nitrates

Class I, LOE A
Aldosterone Antagonist

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Pharmacological Treatment for Stage C HF*r*EF (cont.)

Aldosterone receptor antagonists [or mineralocorticoid receptor antagonists (MRA)] are recommended in patients with NYHA class II-IV and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate >30 mL/min/1.73m2) and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency.

A

Hazard ratio, 0.63 (95% CI, 0.54–0.74)
P<0.001

Hospitalization for Heart Failure or Death from Cardiovascular Causes (%)

Placebo
Eplerenone

Years since Randomization

No. at Risk	0	1	2	3
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

B

Hazard ratio, 0.76 (95% CI, 0.62–0.93)
P=0.008

Death from Any Cause (%)

Placebo
Eplerenone

Years since Randomization

No. at Risk	0	1	2	3
Placebo	1373	947	587	242
Eplerenone	1364	972	625	269

C

Hazard ratio, 0.77 (95% CI, 0.67–0.88)
P<0.001

Hospitalization for Any Reason (%)

Placebo
Eplerenone

Years since Randomization

No. at Risk	0	1	2	3
Placebo	1373	742	403	146
Eplerenone	1364	795	451	179

D

Hazard ratio, 0.58 (95% CI, 0.47–0.70)
P<0.001

Hospitalization for Heart Failure (%)

Placebo
Eplerenone

Years since Randomization

No. at Risk	0	1	2	3
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

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Medical Therapy for Stage C HF*r*EF: Magnitude of Benefit Demonstrated in RCTs

GDMT	RR Reduction in Mortality	NNT for Mortality Reduction (Standardized to 36 mo)	RR Reduction in HF Hospitalizations
ACE inhibitor or ARB	17%	26	31%
Beta blocker	34%	9	41%
Aldosterone antagonist	30%	6	35%
Hydralazine/nitrate	43%	7	33%

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The Game Changer?

A New Novartis Heart Failure Drug

+ Comment Now

As I reported previously (here and here), early on Monday Novartis disclosed that the PARADIGM-HF trial testing LCZ696, a novel, first-in-class Angiotensi... ped early. As I later fo... aid in its press releas... , Milton

"Better is what we need"

I spoke with Clyde Yancy, a leading heart failure ... caution that he has no inside knowledge about this drug or this trial, but he is a knowledgeable observer of the heart failure scene. He was enthusiastic:

> Potentially this is of incredible importance and could really be the breakthrough moment we've been seeking for some time. There has been an ongoing question of whether or not we could ever challenge the primacy of ACE inhibitor therapy in heart failure.

inhibitor. M... s Hospital with long e... ie stopping of a major c... d DSMB [Data and Safety Monitoring Board] as indicating that the final results will be both definitive and important."

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Device Treatment for Stage C HFrEF

From: **Association of Fibrosis With Mortality and Sudden Cardiac Death in Patients With Nonischemic Dilated Cardiomyopathy**

JAMA. 2013;309(9):896-908. doi:10.1001/jama.2013.1363

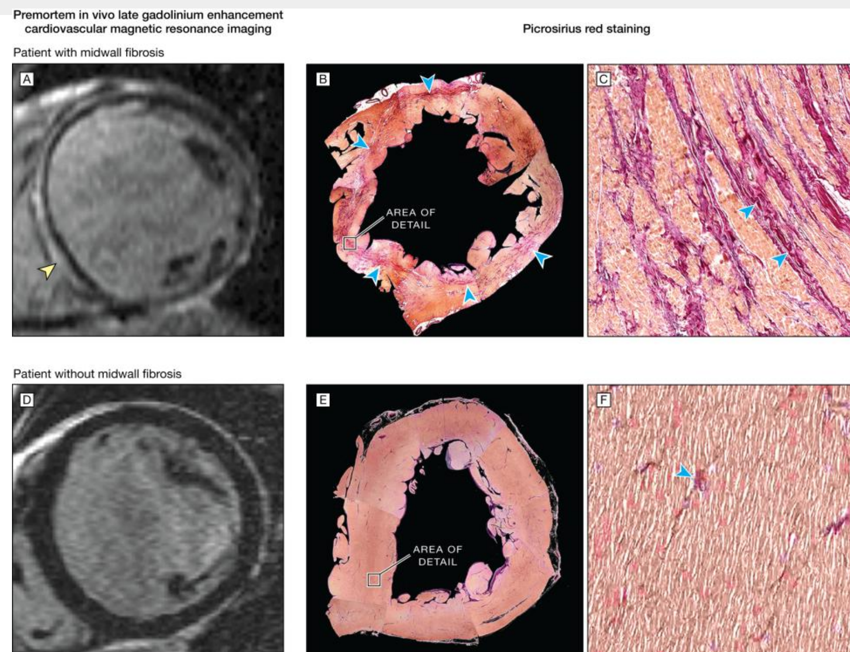

Figure Legend:

A, Premortem late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) demonstrated a near-circumferential pattern of midwall LGE (yellow arrow) in the anterior, septal, inferior, and inferolateral segments at midventricular level. B, Picrosirius red staining in the corresponding postmortem macroscopic short-axis section revealed a prominent linear band of collagen (blue arrows), which mirrored the distribution of LGE on CMR. C, Microscopic examination confirmed the presence of extensive replacement fibrosis (blue arrows) in an area of staining seen on the macroscopic section (area of detail in part B); magnification × 300. D, On LGE-CMR performed prior to cardiac transplantation, there were no areas of LGE. E, Following explantation, macroscopic assessment revealed no detectable regions of collagen with Picrosirius red stain. F, Microscopic section from the septal midwall (area of detail in part E) showed small amounts of perivascular fibrosis (blue arrow) but no replacement fibrosis; magnification × 300. The macroscopic images (B and E) were recomposited from 156 overlapping digital images taken at × 100 magnification with an Olympus digital microscope camera. The image was composited using Microsoft Image Composite Editor (version 1.4.4.0) and Microsoft Office Publisher 2007.

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Date of download: 4/25/2013

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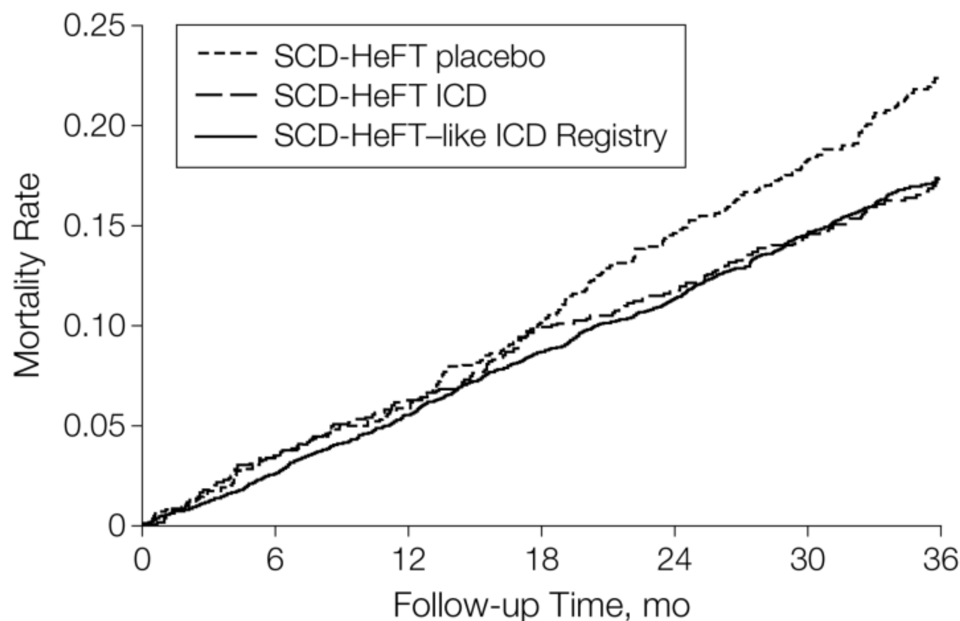
American Heart Association.

From: **Survival of Patients Receiving a Primary Prevention Implantable Cardioverter-Defibrillator in Clinical Practice vs Clinical Trials**

JAMA. 2013;309(1):55-62. doi:10.1001/jama.2012.157182



No. at risk							
SCD-HeFT placebo	847	818	797	761	724	631	504
SCD-HeFT ICD	829	800	778	747	732	611	497
SCD-HeFT–like ICD Registry	3352	3264	3165	3061	2969	2150	1289

Figure Legend:

Patients compared were SCD-HeFT–like patients in the ICD Registry, SCD-HeFT patients randomized to ICD therapy, and SCD-HeFT patients randomized to medical therapy only (for matched patients only). SCD-HeFT indicates Sudden Cardiac Death in Heart Failure Trial; ICD, implantable cardioverter-defibrillator.

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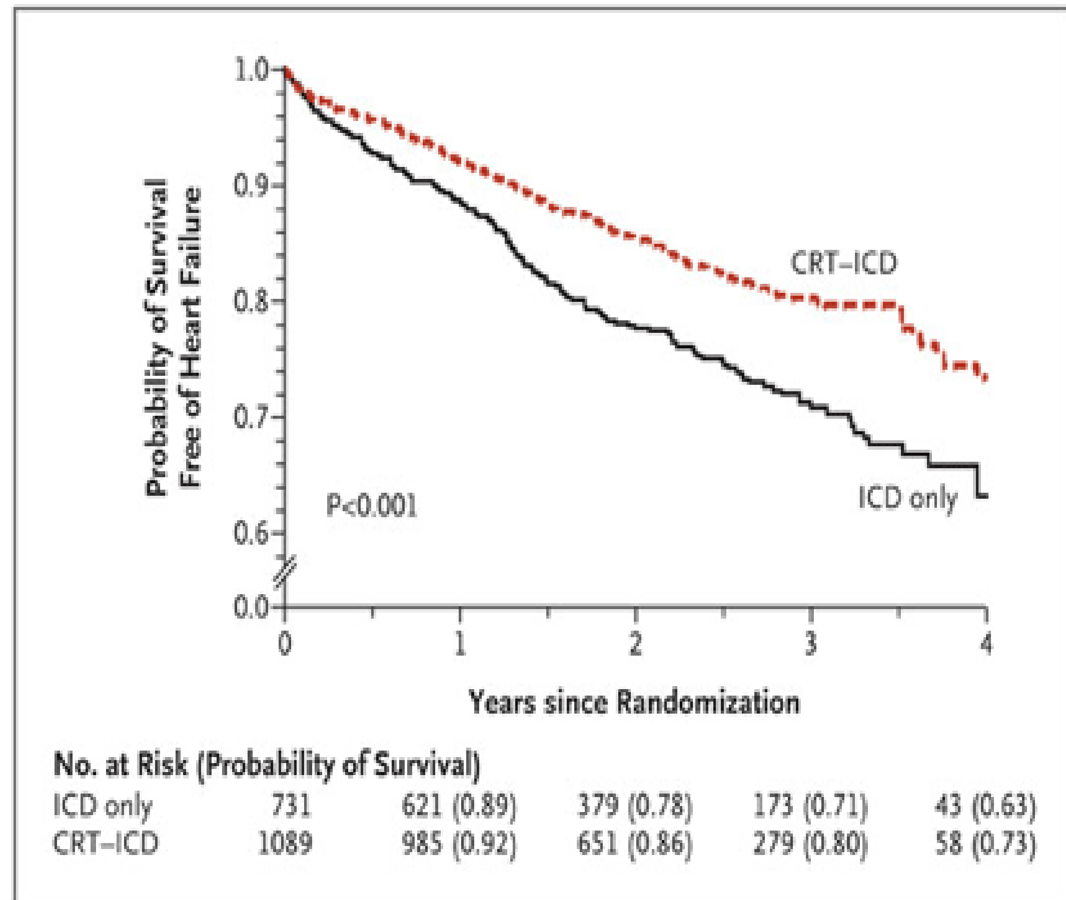
MADIT-CRT (NEJM. 2009)

- **1820 ICM/NICM pts:**
  - **EF ≤ 30%**
  - **QRS ≥ 130 msec**
  - **NYHA I/II**
- **Randomization:**
  - **CRT-D vs. ICD-only**
  - **3:2 ratio**
- **Mean Follow-up:**
  - **2.4 yrs**
- **Outcome:**
  - **HR=0.66 (p=0.001)**



Association.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Cardiac-Resynchronization Therapy in Mild Heart Failure

Ilan Goldenberg, M.D., Valentina Kutyifa, M.D., Ph.D., Helmut U. Klein, M.D., David S. Cannom, M.D., Mary W. Brown, M.S., Ariela Dan, Ph.D., James P. Daubert, M.D., N.A. Mark Estes III, M.D., Elyse Foster, M.D., Henry Greenberg, M.D., Josef Kautzner, M.D., Robert Klempfner, M.D., Malte Kuniss, M.D., Bela Merkely, M.D., Ph.D., Marc A. Pfeffer, M.D., Ph.D., Aurelio Quesada, M.D., Ph.D., Sami Viskin, M.D., Scott McNitt, M.S., Bronislava Polonsky, M.S., Ali Ghanem, M.D., Scott D. Solomon, M.D., David Wilber, M.D., Wojciech Zareba, M.D., Ph.D., and Arthur J. Moss, M.D.

LBBB: ALL-CAUSE MORTALITY

NNT = 9

ICD-only
CRT-D
P=0.002
Probability of Death for LBBB Patients
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0
1
2
3
4
5
6
7
Follow-up Years

Number of Patients at Risk

620	488(.02)	463(.06)	401(.08)	328(.12)	264(.18)	94(.23)	41(.28)
761	734(.02)	714(.03)	638(.07)	627(.08)	426(.12)	167(.16)	70(.18)

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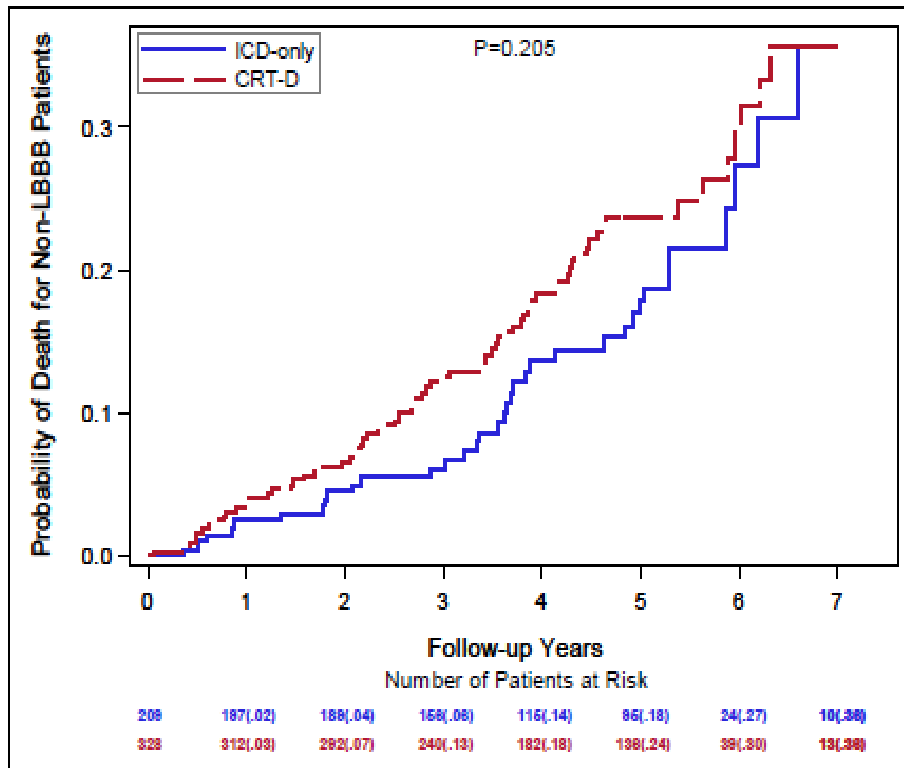
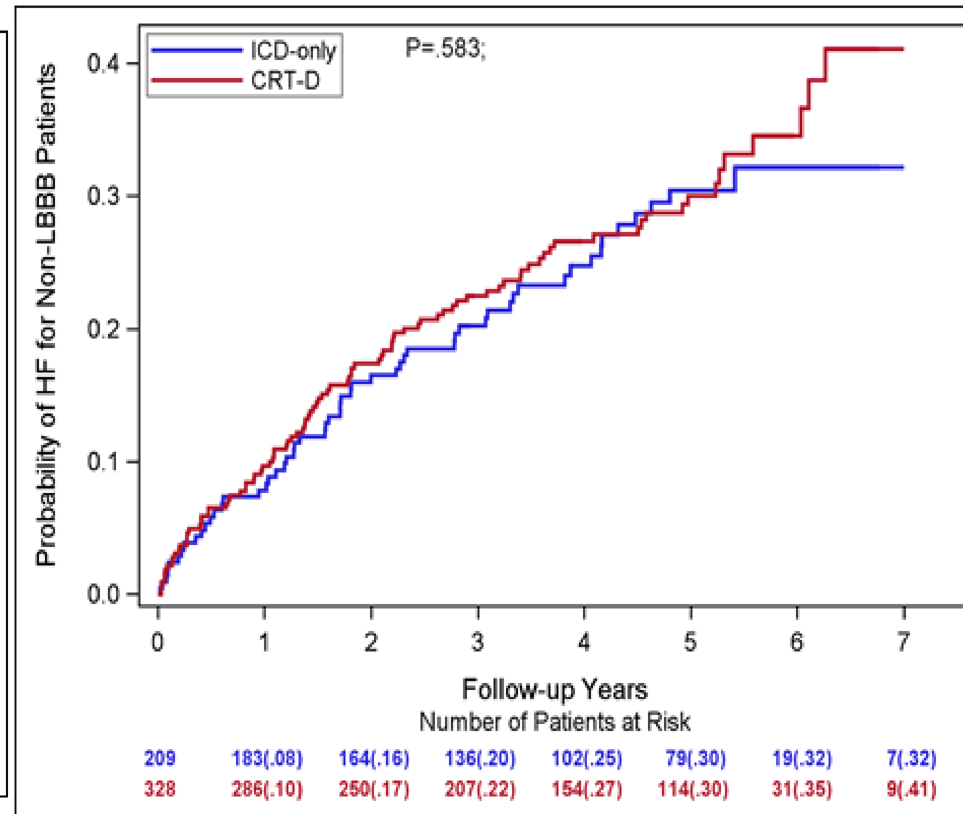
NLBBB

ALL-CAUSE MORTALITY



NON-FATAL HF EVENTS



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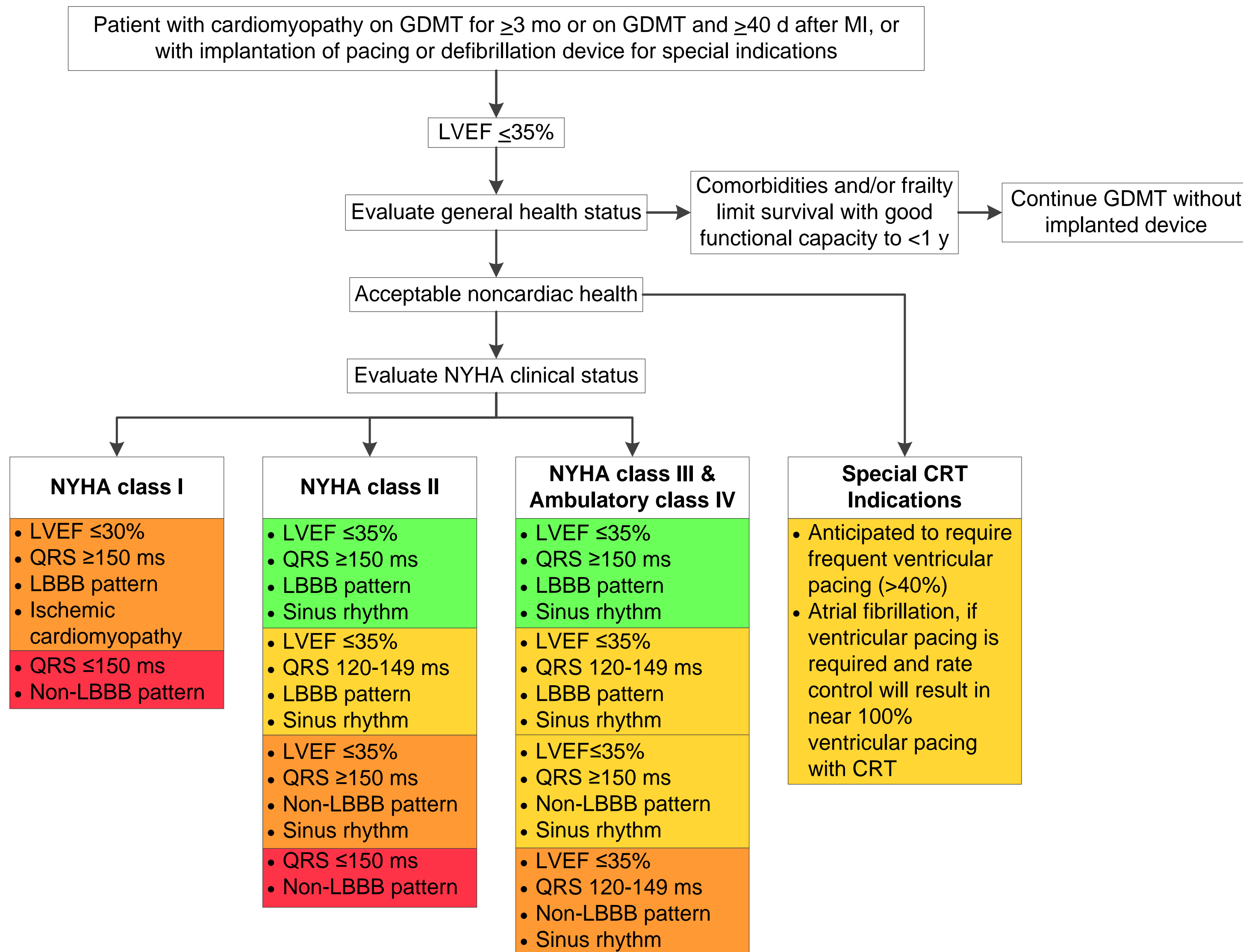
Indications for CRT Therapy



Colors correspond to the class of recommendations in the ACCF/AHA Table 1.

Benefit for NYHA class I and II patients has only been shown in CRT-D trials, and while patients may not experience immediate symptomatic benefit, late remodeling may be avoided along with long-term HF consequences. There are no trials that support CRT-pacing (without ICD) in NYHA class I and II patients. Thus, it is anticipated these patients would receive CRT-D unless clinical reasons or personal wishes make CRT-pacing more appropriate. In patients who are NYHA class III and ambulatory class IV, CRT-D may be chosen but clinical reasons and personal wishes may make CRT-pacing appropriate to improve symptoms and quality of life when an ICD is not expected to produce meaningful benefit in survival.

Inpatient and Transitions of Care

Hospital Discharge

Recommendation or Indication	COR	LOE
Performance improvement systems in the hospital and early postdischarge outpatient setting to identify HF for GDMT	I	B
Before hospital discharge, at the first postdischarge visit, and in subsequent follow-up visits, the following should be addressed: a) initiation of GDMT if not done or contraindicated; b) causes of HF, barriers to care, and limitations in support; c) assessment of volume status and blood pressure with adjustment of HF therapy; d) optimization of chronic oral HF therapy; e) renal function and electrolytes; f) management of comorbid conditions; g) HF education, self-care, emergency plans, and adherence; and h) palliative or hospice care.	I	B
Multidisciplinary HF disease-management programs for patients at high risk for hospital readmission are recommended	I	B
A follow-up visit within 7 to 14 days and/or a telephone follow-up within 3 days of hospital discharge is reasonable	IIa	B
Use of clinical risk-prediction tools and/or biomarkers to identify higher-risk patients is reasonable	IIa	B

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Do the HF clinical practice guidelines actually work?

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Baseline Measure Conformity: Alive vs. Dead at 24-Month Follow-Up

Percent Conformity

100%
80%
60%
40%
20%
0%

	ACEI/ ARB	Beta-blocker	Aldosterone Antagonist	Anti-coagulation for AF	CRT-P/ CRT-D	ICD/ CRT-D	HF Education
Alive at 24-m	82%	88%	35%	72%	40%	52%	61%
Died prior to 24-m follow-up	72%	81%	36%	65%	34%	46%	61%
	p < 0.001	p < 0.001	p = 0.5609	p = 0.0002	p = 0.0384	p < 0.001	p = 0.4751

Alive at 24-m   Died prior to 24-m follow-up

The baseline process measure conformity was significantly lower among patients who died compared with those who survived for 5 of 7 individual measures.

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Fonarow GC, et al. *Circulation*. 2011;123(15):1601-1610

Improved Adherence to HF Guidelines Translates to Improved Clinical Outcomes in Real World Patients

- Each 10% improvement in guideline recommended composite care was associated with a 13% lower odds of 24-month mortality (adjusted OR 0.87; 95% CI, 0.84 to 0.90; *P<0.0001).*

- The adjusted odds for mortality risk for patients with conformity to each measure for which they were eligible was 38% lower than for those whose care did not conform for 1 or more measures for which they were eligible (adjusted OR 0.62; 95% CI, 0.52 to 0.75; *P<0.0001).*

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Fonarow GC, … Yancy, C. *Circulation*. 2011;123:1601-1610.

Incremental Benefit with HF Therapies

(Cumulative % Reduction in Odds of Death at 24 Months Associated with Sequential Treatments)

ACEI/ARB | ACEI/ARB + BB | ACEI/ARB + BB + CRT + ICD

0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
-80%
-90%
-100%

	ACEI/ARB	ACEI/ARB + BB	ACEI/ARB + BB + CRT + ICD
Reduction	-38%	-77%	-90%
Range	+20% to -68%	-43% to -91%	-70% to -96%
P	P=0.1566	P<0.0001	P<0.0001

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Fonarow GC… Yancy CW. *J Am Heart Assoc* 2012;1:16-26.

Results: Mortality Reduction Based on Number of Guideline-Recommended Therapies at Baseline

Number of Therapies (vs 0 or 1 therapy)	Odds Ratio (95% confidence interval)
2 therapies	**0.63** (0.47-0.85) (p=0.0026)
3 therapies	**0.38** (0.29-0.51) (p<0.0001)
4 therapies	**0.30** (0.23-0.41) (p<0.0001)
5, 6, or 7 therapies	**0.31** (0.23-0.42) (p<0.0001)

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Fonarow GC… Yancy CW. *J Am Heart Assoc* 2012;1:16-26.

Heart Failure 2014: It's No Longer about Failure

- We can prevent heart failure
- Evidence-based guideline directed diagnosis, evaluation and therapy should be the mainstay for all patients with heart failure
- Effective implementation of guideline directed best quality care reduces mortality, improves QOL and preserves health care resources
- Ongoing research is needed to answer the remaining questions including: non-pharmacological therapy of HF including dietary adjustments, treatment of HFpEF, management of hospitalized heart failure, effective reduction in HF readmissions, more precise use of device based therapy, and cell based regenerative therapy.

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Northwestern University Feinberg School of Medicine

Northwestern Memorial Hospital