Heart-Failure Management: Update on the New ACC/AHA Guidelines and Future Therapies

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Presenter Disclosure Information

"Heart Failure Guidelines"

I will discuss off label use of medications or devices

DISCLOSURE INFORMATION:
The following relationships exist related to this presentation:

Gregg C. Fonarow, MD, FACC, FAHA
Research: NHLBI, AHQR
Consulting: Amgen, Bayer, Janssen, Novartis, Medtronic, Gambro

Heart Failure Background

Population Group	Prevalence	Incidence	Mortality	Hospital Discharges	Cost
Total population	5,100,000	825,000	50% at 5 years	1,023,000	$30.7 billion

- Heart failure (HF) is a major public health problem resulting in substantial morbidity, mortality, and healthcare expenditures
- Major cost-driver of HF is high incidence of hospitalizations
- Despite treatment advances large number of eligible patients are not receiving one or more evidence-based HF therapies

American Heart Association. *2014 Heart and Stroke Statistical Update.* Dallas, Tex: American Heart Association; 2014

Evidence Based Care for HF

- Evidence based guidelines are based on rigorous and expert analysis of available data documenting relative benefits and risks of procedures and therapies
- The ACC/AHA practice guidelines reflect a consensus of expert opinion and are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions
- These guidelines are intended to help improve the effectiveness of care, optimize patient outcomes, and favorably affect the overall cost of care by focusing resources on the most effective strategies

ACCF/AHA Heart Failure Guideline 2013 Writing Committee Members

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J Am Coll Cardiol. 2013;62:1495-1539.

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AHA/ACC Applying Classification of Recommendations and Level of Evidence

Class I	Class IIa	Class IIb	Class III
Benefit >>> Risk	*Benefit >> Risk Additional studies with focused objectives needed*	*Benefit ≥ Risk Additional studies with broad objectives needed; Additional registry data would be helpful*	*Risk ≥ Benefit No additional studies needed*
Procedure or treatment **SHOULD** be performed or administered	**IT IS REASONABLE** to perform procedure or administer treatment	Procedure or treatment **MAY BE CONSIDERED**	Procedure or treatment should **NOT** be performed or administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**

Level of Evidence

A: Multiple randomized controlled trials
B: Single trial, non-randomized studies
C: Expert opinion

Yancy CW et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

What's New in the 2013 Guideline?

- Revision in classification based on EF
- Evidence-based drug selection and dosing
- Expanded or refined recommendations
  - Aldosterone antagonists
  - Fixed-dose nitrate and hydralazine combination
  - Omega 3 fatty acids
  - Cardiac resynchronization therapy (CRT)
  - Biomarkers for diagnosis and risk stratification

Yancy CW et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Approach to the Classification of Heart Failure

At Risk

Heart Failure

Stage		Patient Description
A	High risk for developing heart failure (HF)	▪ Hypertension ▪ CAD ▪ Diabetes mellitus ▪ Family history of cardiomyopathy
B	Asymptomatic HF	▪ Previous MI ▪ LV systolic dysfunction ▪ Asymptomatic valvular disease
C	Symptomatic HF	▪ Known structural heart disease ▪ Shortness of breath and fatigue ▪ Reduced exercise tolerance
D	Refractory end-stage HF	▪ Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

Yancy CW et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Classification of Heart Failure

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF.	None	
B	Structural heart disease but without signs or symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions.		

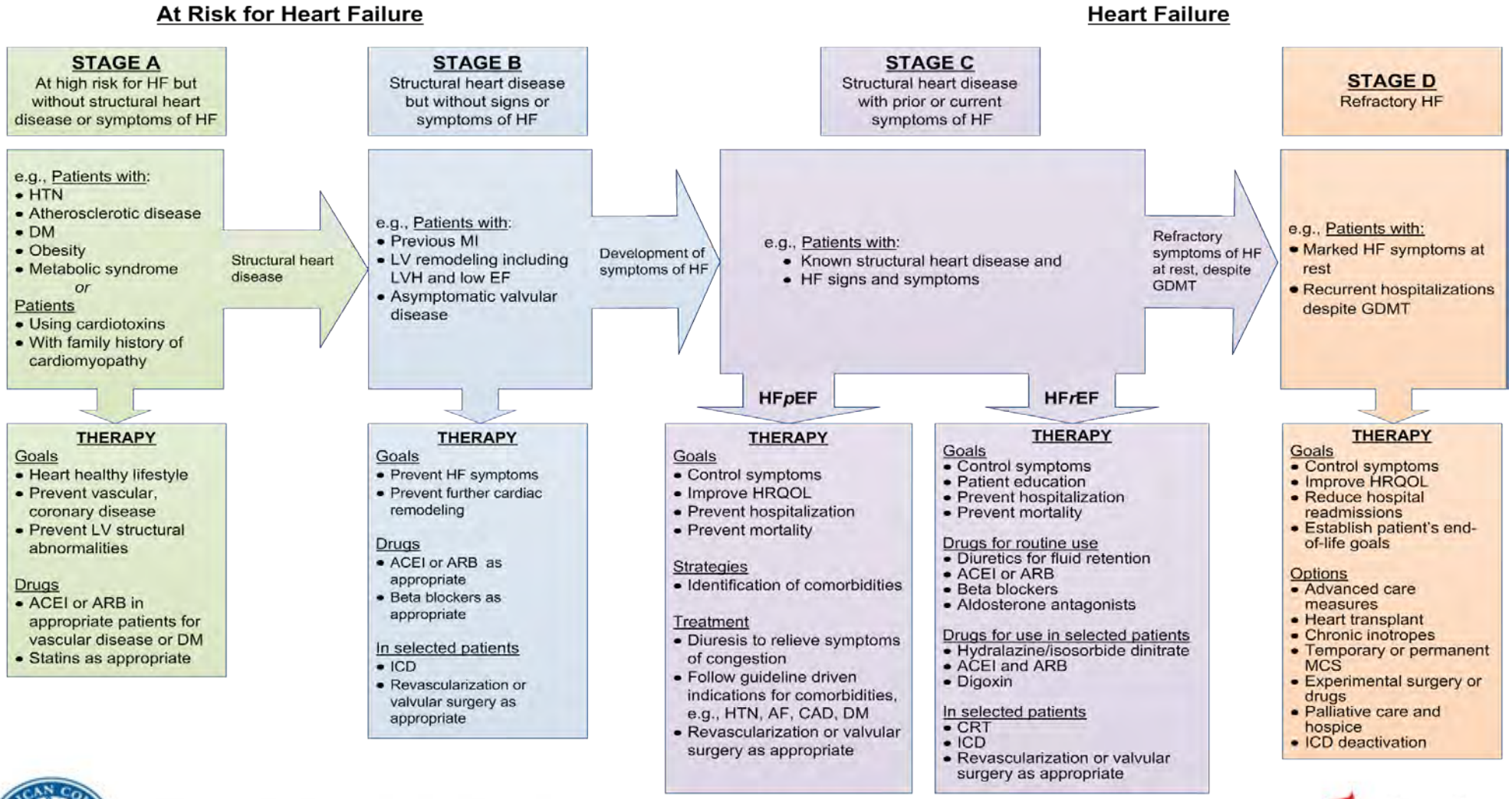
Yancy CW et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

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.

Yancy CW et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Stages, Phenotypes and Treatment of HF



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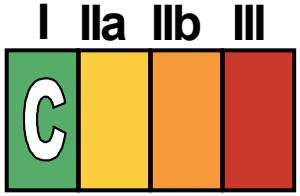
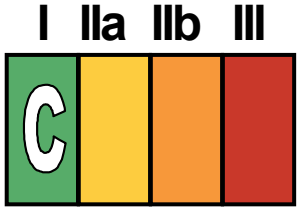
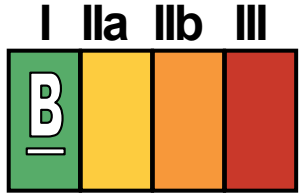
History and Physical Examination



A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF.



In patients with idiopathic DCM, a 3-generational family history should be obtained to aid in establishing the diagnosis of familial DCM.



Volume status and vital signs should be assessed at each patient encounter. This includes serial assessment of weight, as well as estimates of jugular venous pressure and the presence of peripheral edema or orthopnea.

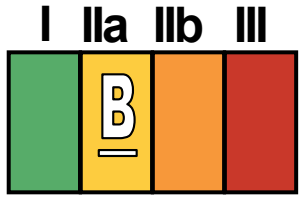
Recommendations for Noninvasive Imaging

Recommendation	COR	LOE
Patients with suspected, acute, or new-onset HF should undergo a chest x-ray	I	C
A 2-dimensional echocardiogram with Doppler should be performed for initial evaluation of HF	I	C
Repeat measurement of EF is useful in patients with HF who have had a significant change in clinical status or received treatment that might affect cardiac function, or for consideration of device therapy	I	C
Noninvasive imaging to detect myocardial ischemia and viability is reasonable in HF and CAD	IIa	C
Viability assessment is reasonable before revascularization in HF patients with CAD	IIa	B
Radionuclide ventriculography or MRI can be useful to assess LVEF and volume	IIa	C
MRI is reasonable when assessing myocardial infiltration or scar	IIa	B
Routine repeat measurement of LV function assessment should not be performed	III: No Benefit	B

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

Risk Scoring



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

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Recommendations for Invasive Evaluation

Recommendation	COR	LOE
Monitoring with a pulmonary artery catheter should be performed in patients with respiratory distress or impaired systemic perfusion when clinical assessment is inadequate	I	C
Invasive hemodynamic monitoring can be useful for carefully selected patients with acute HF with persistent symptoms and/or when hemodynamics are uncertain	IIa	C
When coronary ischemia may be contributing to HF, coronary arteriography is reasonable	IIa	C
Endomyocardial biopsy can be useful in patients with HF when a specific diagnosis is suspected that would influence therapy	IIa	C
Routine use of invasive hemodynamic monitoring is not recommended in normotensive patients with acute HF	III: No Benefit	B
Endomyocardial biopsy should not be performed in the routine evaluation of HF	III: Harm	C

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

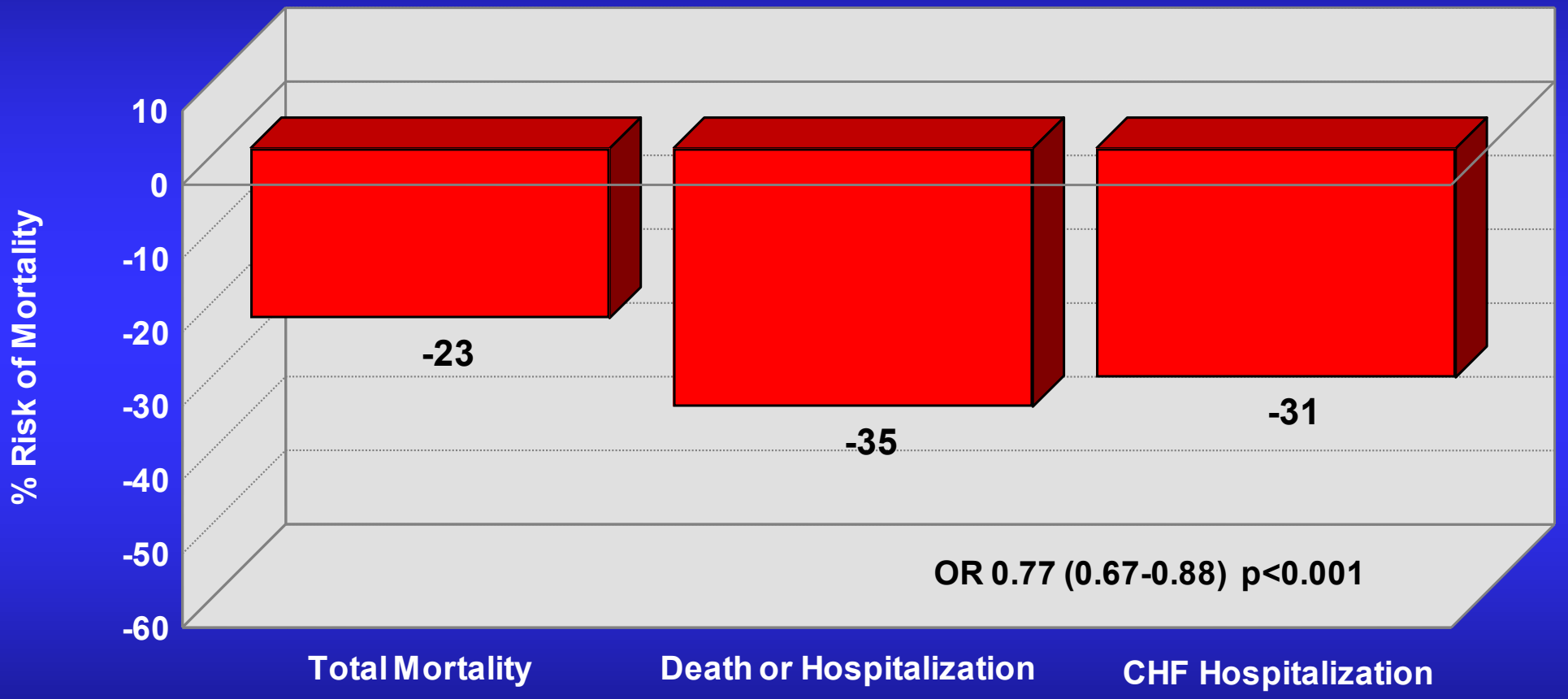
ACC/AHA HF Guidelines: Management of Heart Failure (Stage C)

Life Prolonging Medical Therapy

- ACE inhibitors or ARB (Class I, evidence A) all patients without contraindications or intolerance
- β-Blockers (Class I, evidence A) all patients without contraindications or intolerance
- Aldosterone antagonists (Class I, evidence A) all patients with Class II-IV HF without contraindications or intolerance, when close monitoring can be assured

Yancy CW et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Effect of ACE Inhibitors on Mortality and Hospitalizations in Patients with HF



32 Trials of ACEI in Heart Failure ACEI (n = 3870) Placebo (n = 3235)
Collaborative Group on ACE Inhibitor Trails JAMA 1995;273:1450-1456

Effect of ACE Inhibitors on Mortality and Hospitalizations in Patients with HF

Subgroup	ACE Inhibitor	Controls	OR
Male	22.9	33.2	0.63
Female	20.2	29.5	0.78
< 60	22.2	31.1	0.71
> 60	24.9	36.9	0.79
Class I	17.5	24.8	0.69
Class II	19.5	28.4	0.68
Class III	22.1	43.2	0.58
Class IV	46.2	59.2	0.69
Ischemic	28.3	40.1	0.63
Nonischemic	23.2	29	0.72
LVEF >25	23.6	29.6	0.85
LVEF < 25	33.7	48	0.53
All Patients	22.4	32.6	0.65

Total Mortality or Hospitalization for Congestive Heart Failure

32 Trials of ACEI in Heart Failure ACEI (n = 3870) Placebo (n = 3235)
Collaborative Group on ACE Inhibitor Trails JAMA 1995;273:1450-1456

High vs Low Dose ACEI Therapy for Heart Failure

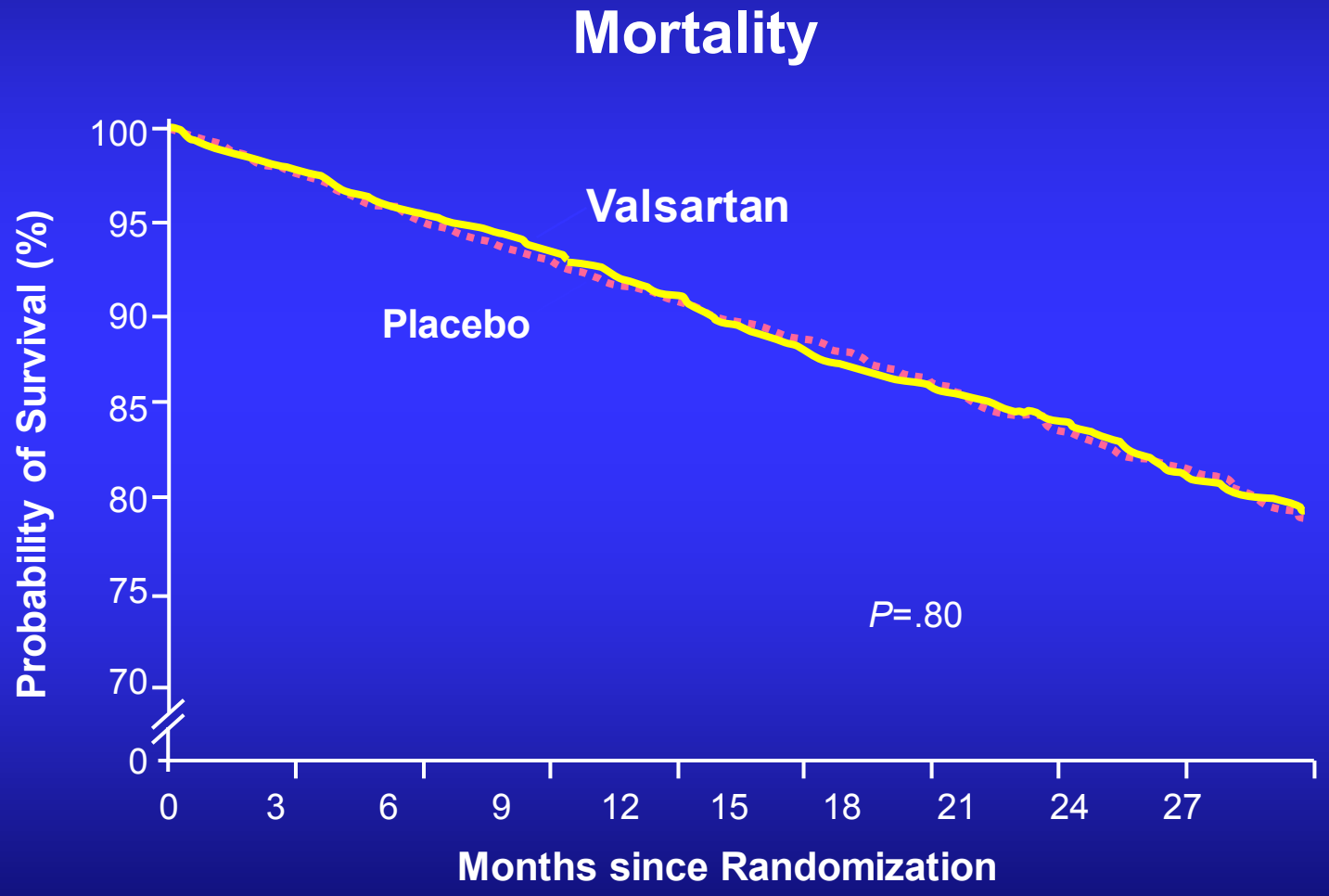
	Low Dose	High Dose	OR	
Death or Hospitalization	1339/1596 83.9%	1251/1568 79.8%	0.88 (0.82-0.95)	p=0.002
Death	717/1596 44.9%	666/1568 42.5%	0.92 (0.81-1.03)	p=0.128

ATLAS: 8% reduction in death and 14% reduction in death and HF hospitalization
SOLVD: 14% reduction in death and 26% reduction in death and HF hospitalization

3164 patients with Class II-IV CHF ave f/u 46 months
Lisinopril Low Dose 2.5 to 5.0 mg/d High Dose 32.5 to 35.0 mg/d

Packer Circulation 1999;100:1-7

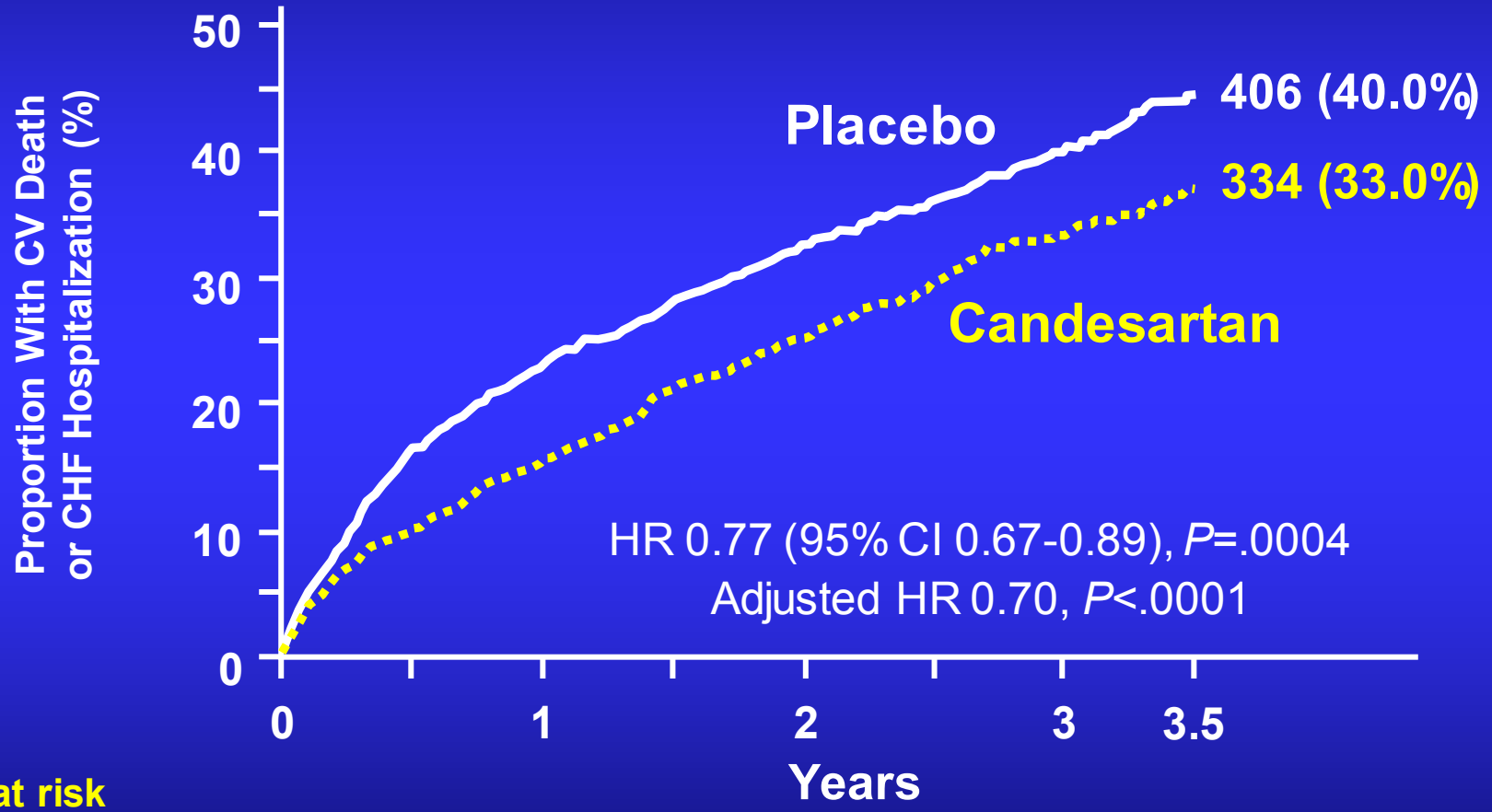
ValHeFT: ARB added to Standard HF Care Including ACEI



Cohn J et al. *N Engl J Med.* 2001;345:1667–1675.

CHARM-Alternative

Primary outcome of CV death or CHF hospitalization



Number at risk					
Candesartan	1,013	929	831	434	122
Placebo	1,015	887	798	427	126

Granger CB, et al. *Lancet*. 2003;362:772-776.

ACEI/ARB in Heart Failure

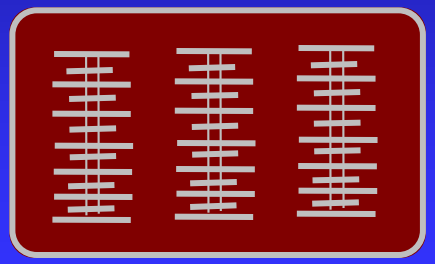
- Indicated for all patients with asymptomatic LV dysfunction and for Class I to IV heart failure. (Contraindications: hyperkalemia, angioedema, pregnancy)
- Titrate to target doses (example enalapril 10 mg bid, lisinopril 20 qd, ramipril 10 mg qd, benazepril 40 qd valsartan 160 mg bid, candesartan 32 mg qd)
- Monitor serum potassium and renal function. Advise checking chemistry panel 1-2 weeks after first dose
- Combination of ACE inhibitor with ARB may be considered in persistently symptomatic patient, but only if not candidate for aldosterone antagonist

Yancy CW et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Drugs Commonly Used for HF*r*EF (Stage C HF)

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials
ACE Inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	122.7 mg/d (421)
Enalapril	2.5 mg twice	10 to 20 mg twice	16.6 mg/d (412)
Fosinopril	5 to 10 mg once	40 mg once	---------
Lisinopril	2.5 to 5 mg once	20 to 40 mg once	32.5 to 35.0 mg/d (444)
Perindopril	2 mg once	8 to 16 mg once	---------
Quinapril	5 mg twice	20 mg twice	---------
Ramipril	1.25 to 2.5 mg once	10 mg once	---------
Trandolapril	1 mg once	4 mg once	---------
ARBs			
Candesartan	4 to 8 mg once	32 mg once	24 mg/d (419)
Losartan	25 to 50 mg once	50 to 150 mg once	129 mg/d (420)
Valsartan	20 to 40 mg twice	160 mg twice	254 mg/d (109)
Aldosterone Antagonists			
Spironolactone	12.5 to 25 mg once	25 mg once or twice	26 mg/d (424)
Eplerenone	25 mg once	50 mg once	42.6 mg/d (445)

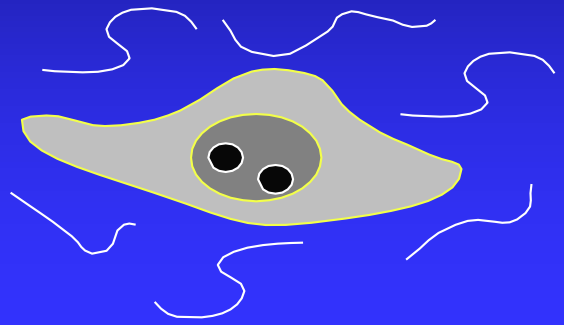
Effects of Aldosterone



Cardiac Myocyte

Hypertrophy

Norepinephrine Release



Fibroblast

Hyperplasia

Collagen Synthesis

Fibrosis

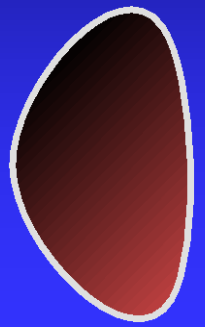
Peripheral Artery

Vasoconstriction

Endothelial Dysfunction

Hypertrophy

Decreased Compliance

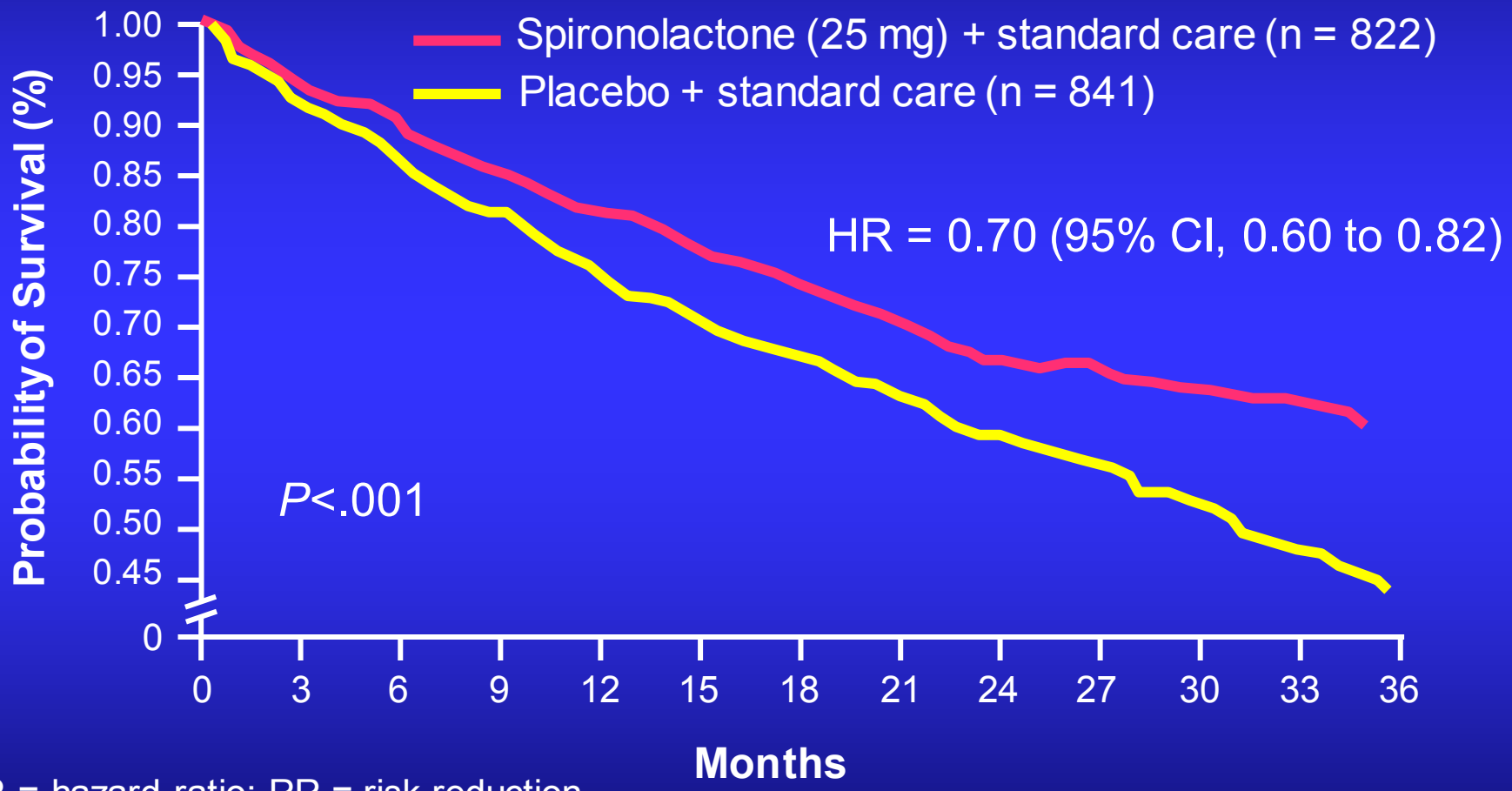


Kidney

Potassium Loss

Sodium Retention

RALES: Aldosterone Antagonist Reduces All-Cause Mortality in Chronic HF



HR = hazard ratio; RR = risk reduction.

*Ejection fraction ≤35% Class III or IV symptoms at some point in prior 2 months.

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

RALES Results: Relative Risks of Various End Points Related to Death or Hospitalization in the Spironolactone Group

End point	Relative Risk (95% CI)	p
Death from Cardiac Causes or Hospitalization for Cardiac Causes	0.68 (0.59-0.78)	<0.001
Death from Any Cause or Hospitalization for Any Reason	0.77 (0.68-0.86)	<0.001
Death from Any Cause or Hospitalization for Cardiac Causes	0.68 (0.60-0.77)	<0.001
Cause of Death		
Cardiac Causes	0.69 (0.58-0.82)	<0.001
Progression of Heart Failure*	0.64 (0.51-0.80)	<0.001
Sudden Death†	0.71 (0.54-0.95)	0.02
Reason for hospitalization		
All Cardiac Causes‡	0.70 (0.59-0.82)	<0.001
Worsening Heart Failure	0.65 (0.54-0.77)	<0.001

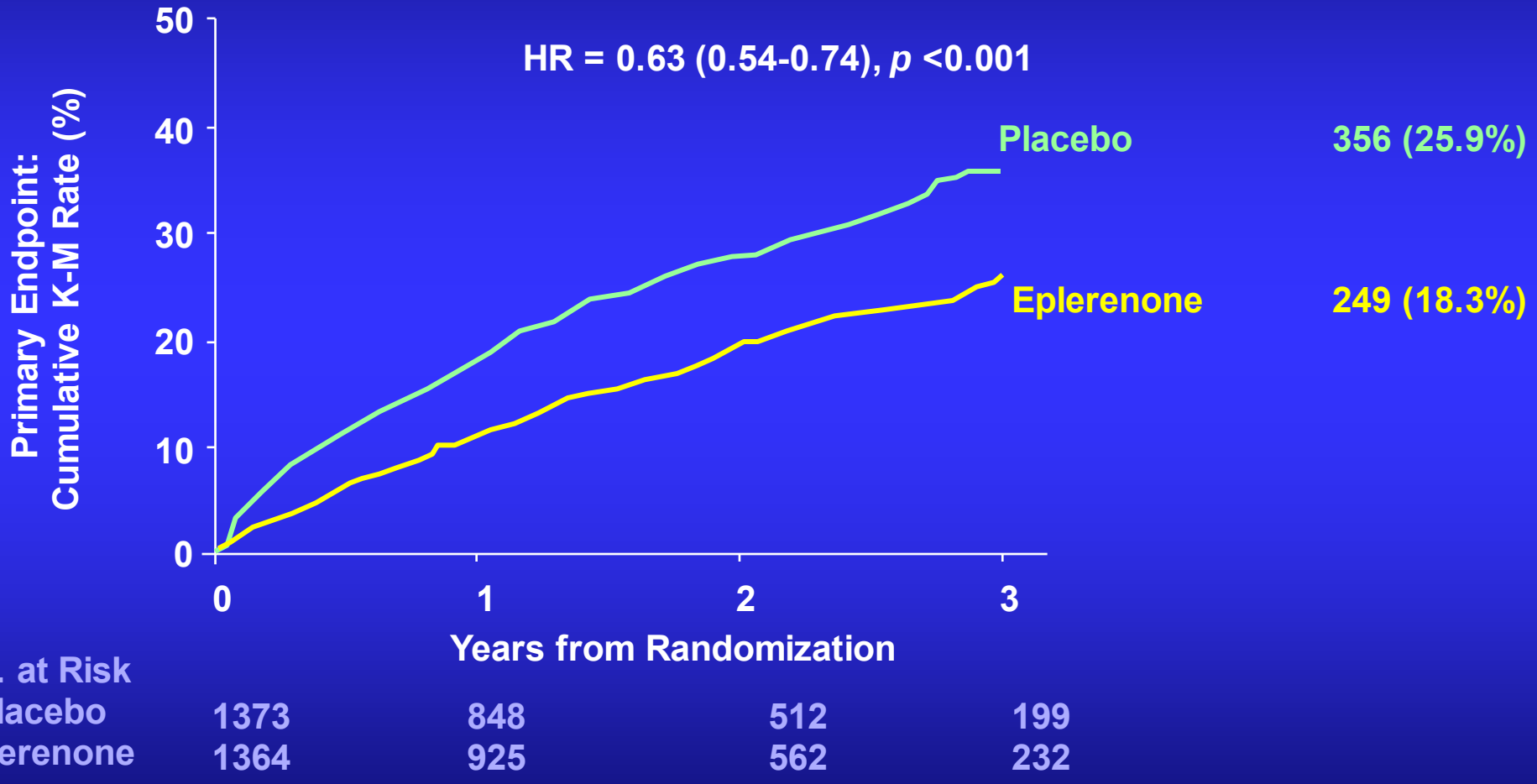
† This category includes death due to worsening heart failure (defined as increasing symptoms or signs requiring an increase in treatment).

† This category includes witnessed death from cardiac causes heralded by abrupt loss of consciousness within one hour after the onset of symptoms in a patient in whom death was unexpected.

‡ Some patients were hospitalized for more than one cardiac cause.

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms: EMPHASIS HF

Primary Endpoint: CV Mortality and HF Hospitalization



Zannad F. New Engl J Med. 2011;364:11-21.

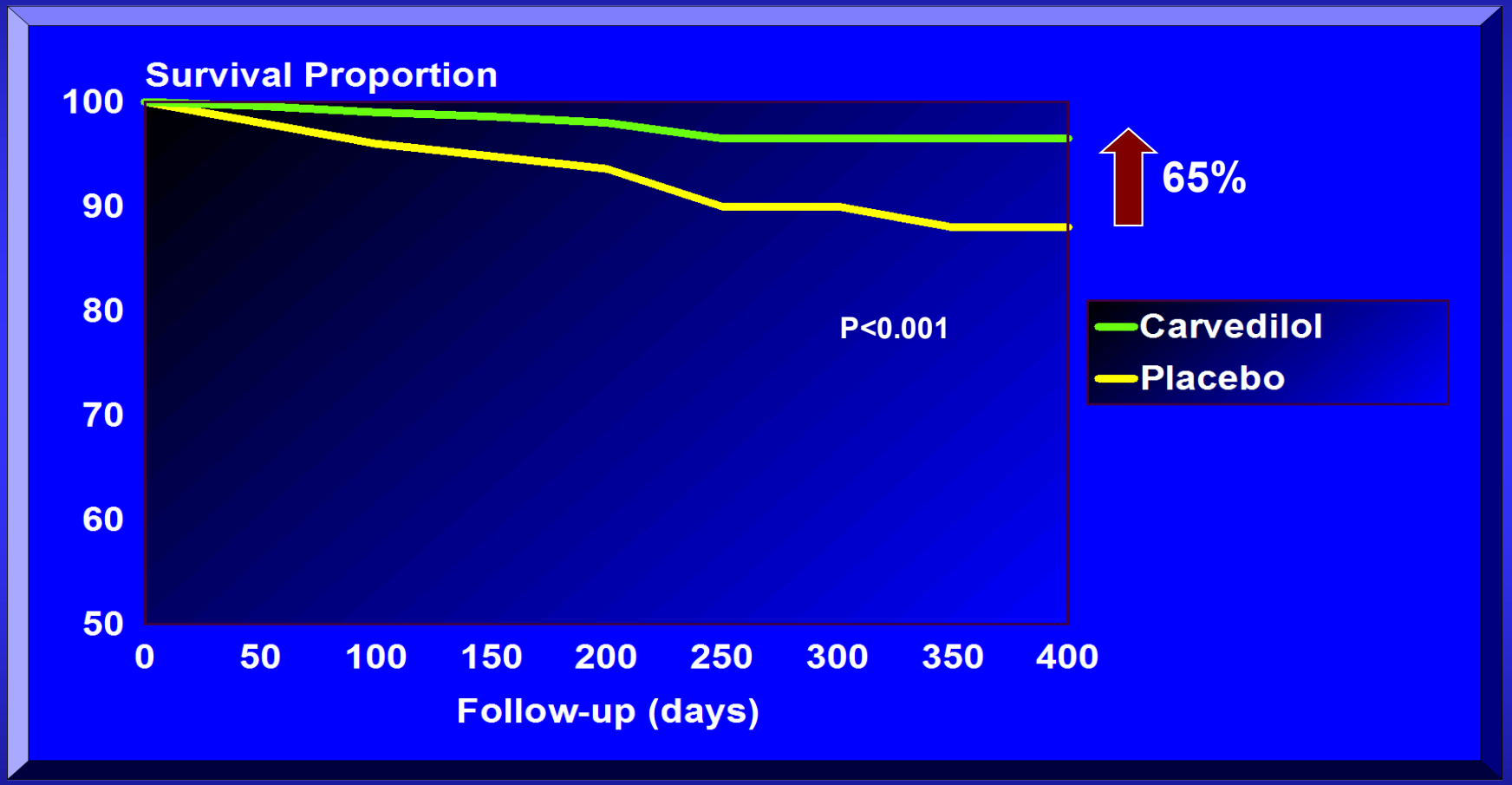
Aldosterone Antagonists in Heart Failure

- Indicated for patients with Class II-IV HF due to rEF (LVEF ≤ 0.40). (Contraindications: hyperkalemia, Cr > 2.5 in men and > 2.0 in women)
- Spironolactone 12.5 mg PO qd starting dose (or 6.25 mg in higher risk patients) or Eplerenone 25 mg qd. Decrease potassium supplementation and loop diuretic dose at time of initiation.
- Critical to very closely monitor serum potassium and renal function. Advise checking chemistry panel at 48 hours, 1 week, and 4 weeks.
- Advance Spironolactone dose at 4 weeks to 25 mg PO qd or Eplerenone 50 mg which is the target dose. Avoid higher doses due to risk of hyperkalemia.

Yancy CW et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Effect of Carvedilol in Heart Failure

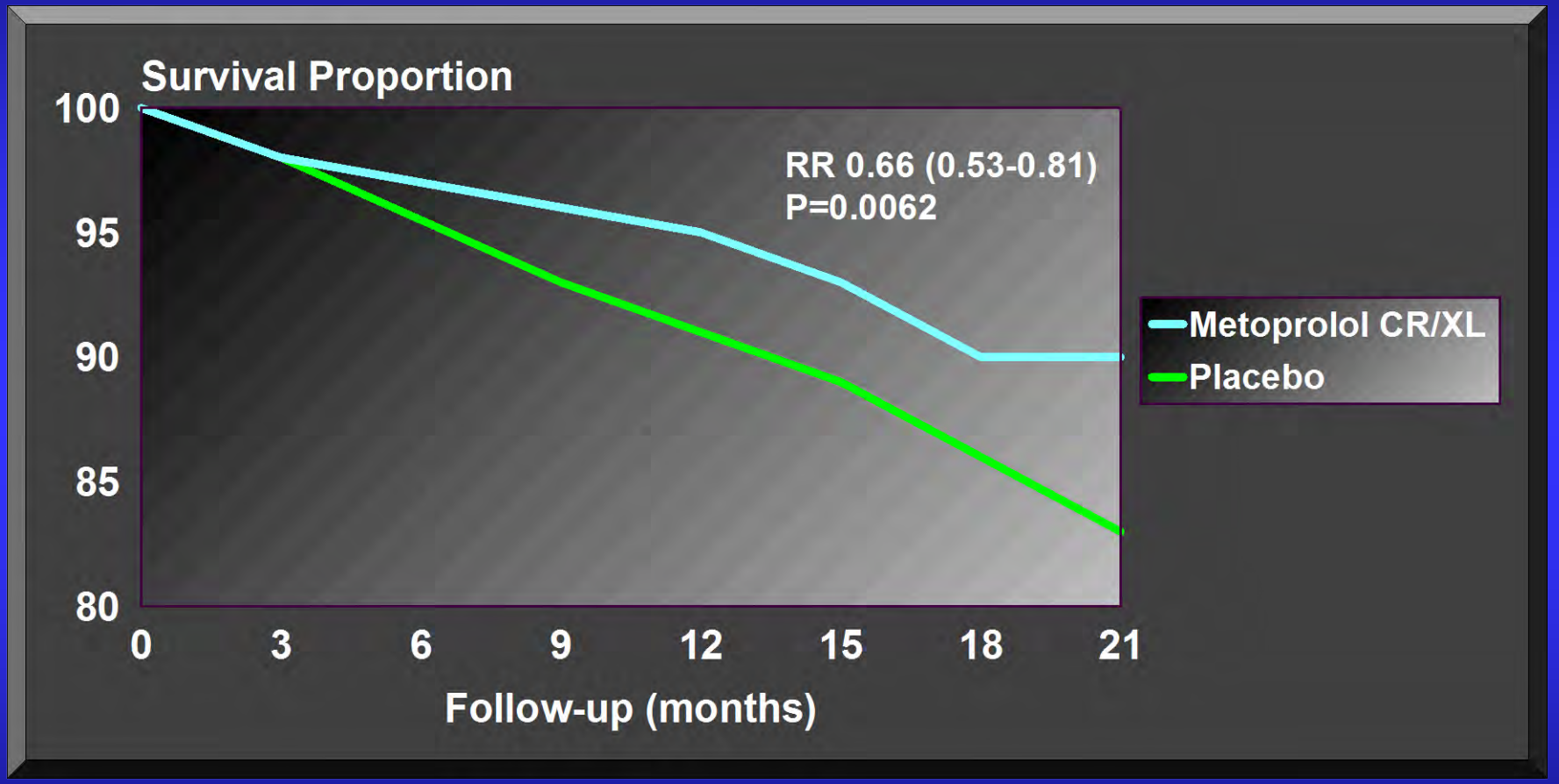
US Heart Failure Trials Program



1094 Class II-IV CHF pts on triple therapy (ACEI, digoxin, diuretics)
Carvedilol 6.25 bid test 2 weeks, then 12.5 bid, then 25 bid vs placebo
Packer NEJM 1996;334:1349-55

Effect of Metoprolol CR/XL in Heart Failure

MERIT-HF



3991 pts with CHF Class II-IV, ave age 64 and LVEF 0.28
Randomized to Metoprolol CR/XL 12.5 mg or 25 mg PO qd, target dose 200 mg qd
Lancet 1999;353:2001-07

Major Trials of β-Blockade in Heart Failure

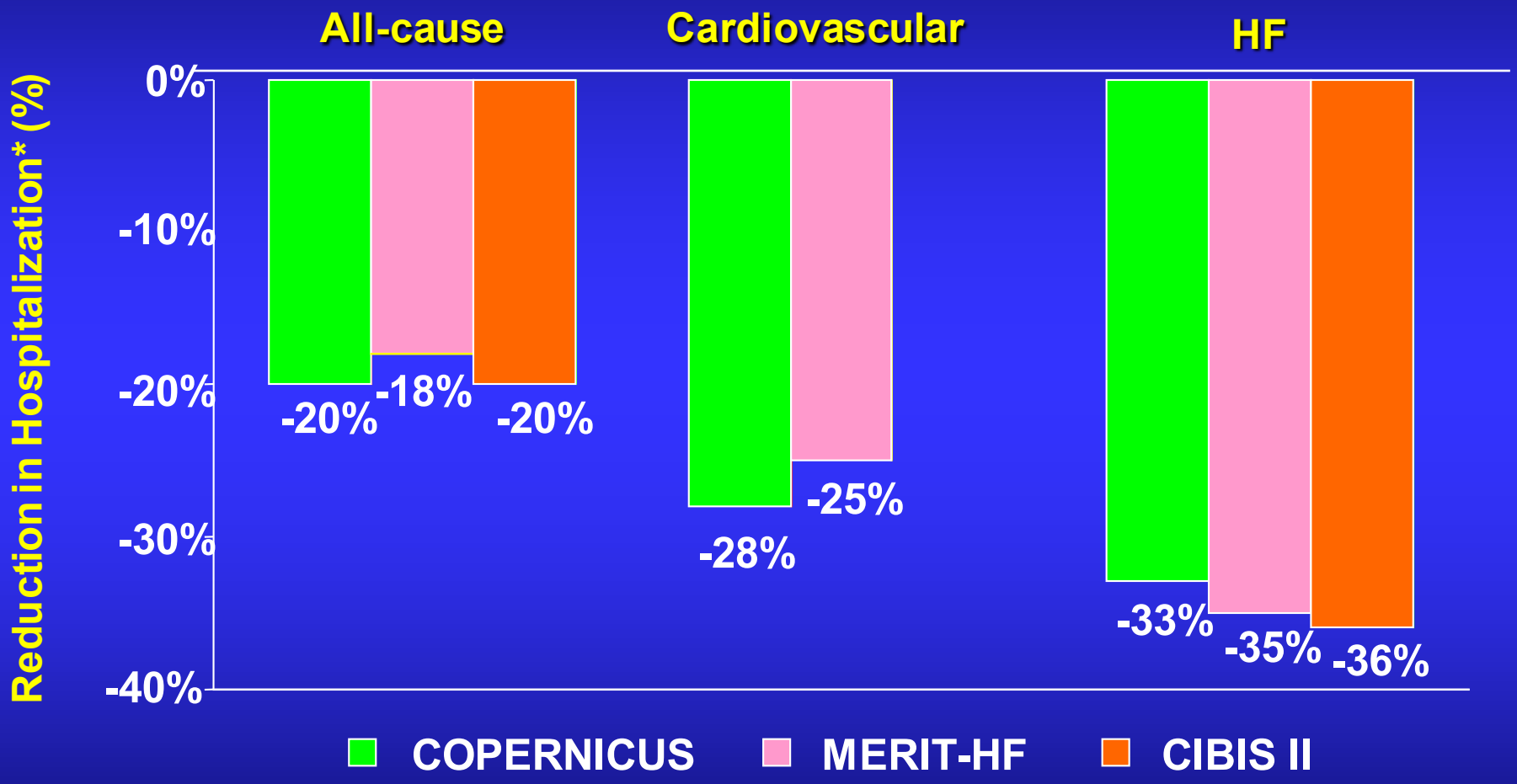
	Patients (n)	Follow-up (yrs)	NYHA Class	LVEF (%)	Effects on Outcomes
CIBIS	641	1.9	II-III	≤ 35	All-cause mortality: ↓ 22% NS
CIBIS-II	2647	1.3	II-III	≤ 35	All-cause mortality: ↓ 34% (*P*<.0001)
MDC	383	1	II-III	≤ 40	Death or need for transplant: ↓ 30%, P<0.05
MERIT-HF	3991	1	II-III	≤ 40	All-cause mortality: ↓ 34% (*P*=.0062)
US Carvedilol Trials	1094	7.5 months	II-III	≤ 35	All-cause mortality*: ↓ 65% (*P*=.0001)
COPERNICUS	2289	10.5 months	IV	≤ 25	

Effect of Carvedilol in Severe Heart Failure

COPERNICUS

2289 Class IV CHF pts, LVEF < 0.25, (not on inotropes x 4days) ave age 63, LVEF 0.20
Carvedilol 3.125 bid, q 2 wks titration. 75% to target. withdrawl 16% placebo, 13% carvedilol
Packer NEJM 2001;344:1651-8

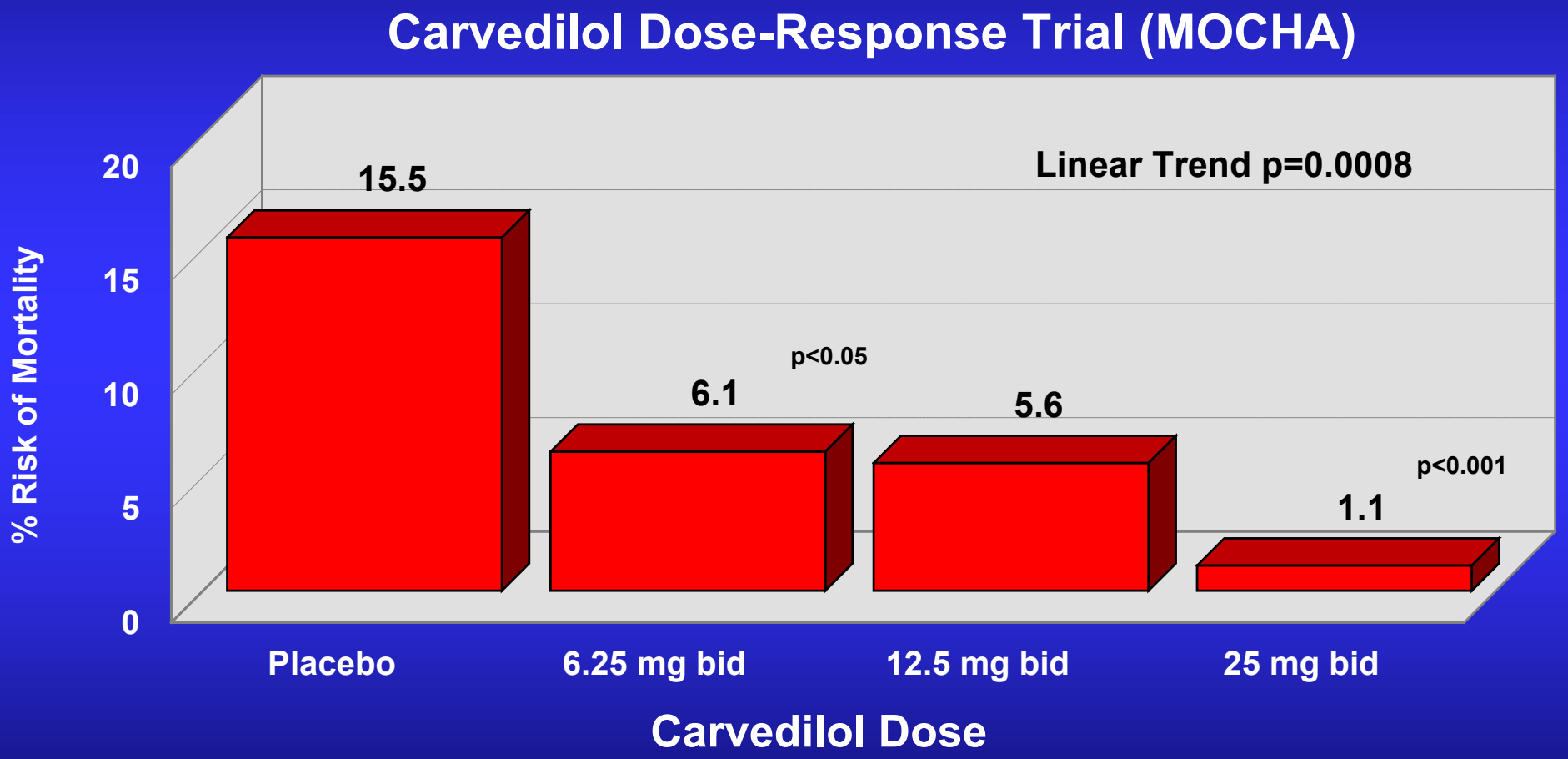
Effect of β-Blockade on Hospitalizations



Only carvedilol and metoprolol CR/XL are FDA approved for HF therapy in the U.S.

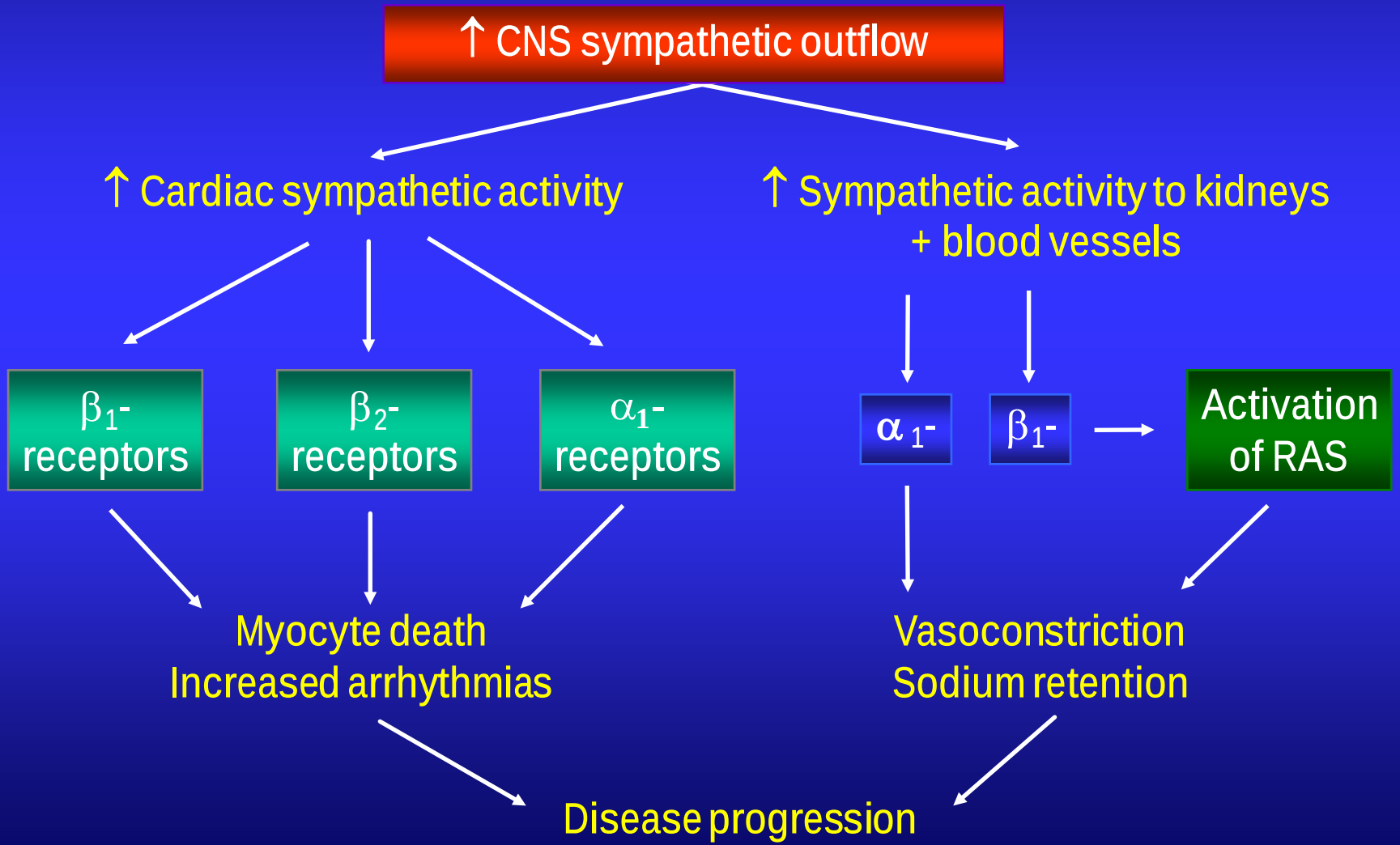
[1]Packer M et al. *N Engl J Med*. 2001;344:1651–1658. [2]Hjalmarson A et al. *JAMA*. 2000;283:1295–1302.
[3]CIBIS II Investigators. *Lancet.* 1999;353:9–13.

Effect of Carvedilol Dose on Mortality in Patients with Heart Failure



Dose Response of Carvedilol in moderate heart failure patients on all cause mortality
Bristow Circulation 1996;94:2807

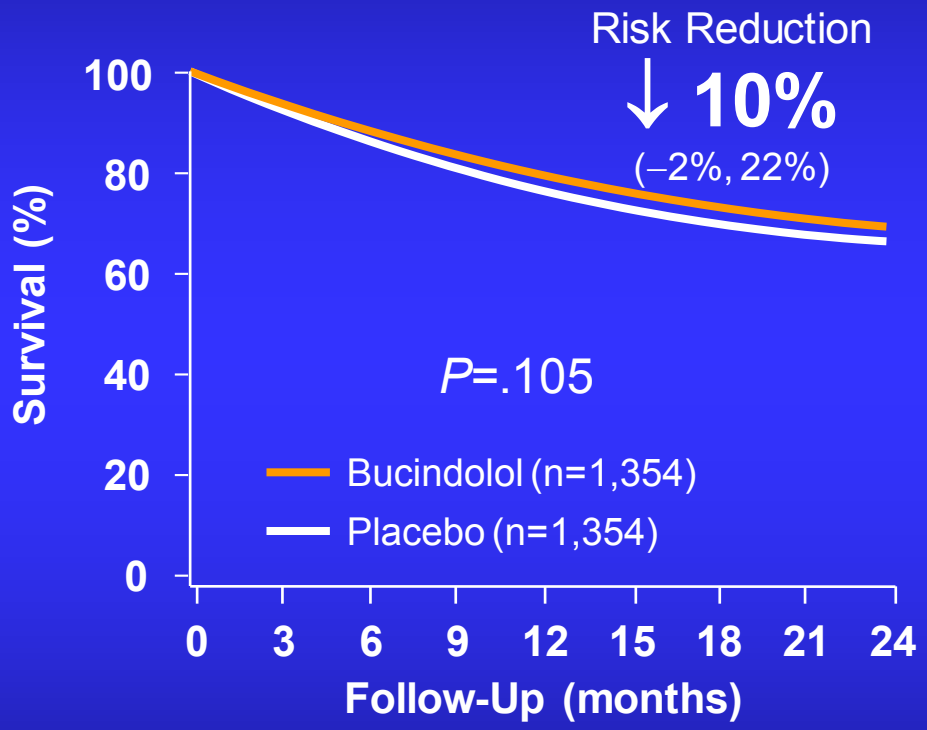
Effects of Sympathetic Activation in Heart Failure



Bristow MR. *Circulation*. 2000;101:558-569.

Not All β-Blockers Reduce Mortality in HF

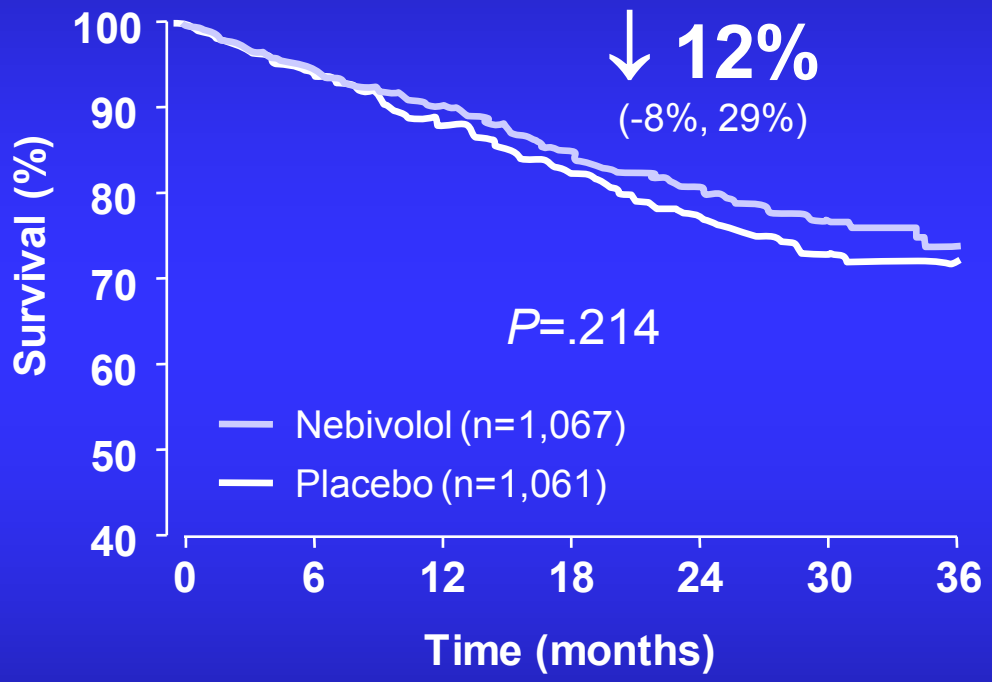
BEST[1]



2,708 patients (CHF Class III–IV, average age 60, LVEF .23) randomized to placebo or bucindolol (3 mg titrated to 50 mg po BID).

Number of events: bucindolol 411 (30%); placebo 449 (33%).

SENIORS[2]



2,128 patients (CHF Class II–III, average age 76, average LVEF .36 with approximately 65% of patients with LVEF ≤.35) randomized to Placebo or nebivolol (1.25 mg titrated to 10 mg po QD). All-cause mortality was a secondary endpoint.

Number of events: nebivolol 169 (15.8%); placebo 192 (18.1%).

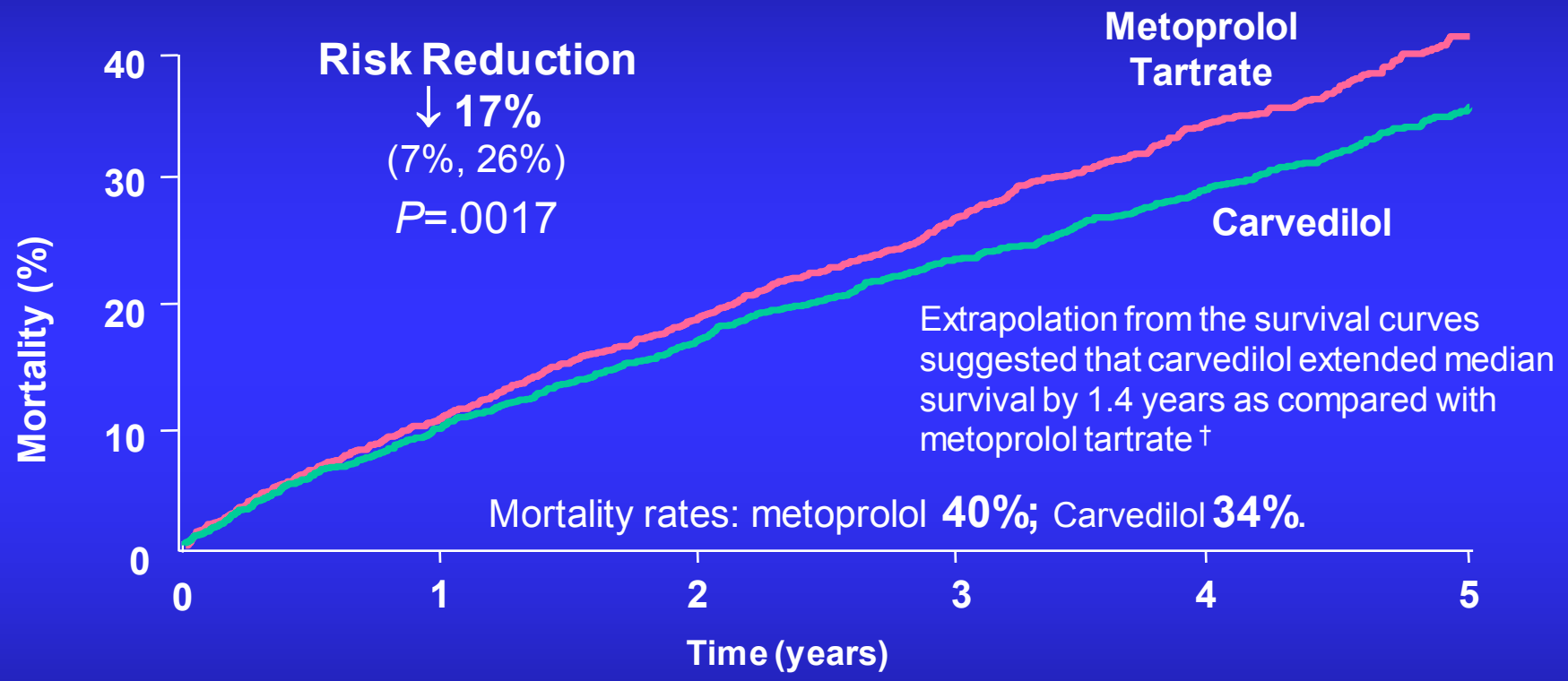
[1]BEST Investigators. *N Engl J Med*. 2001;344:1659-1667. [2]Flather, M et al. *Eur Heart J*. 2005;26:215-225.

β-Blockers Differ in Their Long-Term Effects on Mortality in HF

Bisoprolol[1]	Beneficial
Bucindolol[2]	No effect
Carvedilol[3-5]	Beneficial
Metoprolol tartrate[6]	Not well studied
Metoprolol succinate[7]	Beneficial
Nebivolol[8]	No effect
Xamoterol[9]	Harmful

[1]CIBIS II Investigators and Committees. *Lancet.* 1999;353:9-13. [2]The BEST Investigators. *N Engl J Med* 2001; 344:1659-1667. [3]Colucci WS, et al. *Circulation* 1996;94:2800-2806. [4]Packer M, et al. *N Engl J Med* 2001;344:1651-1658. [5]The CAPRICORN Investigators. *Lancet.* 2001;357:1385-1390. [6]Waagstein F, et al. *Lancet.* 1993;342:1441-1446. [7]MERIT-HF Study Group. *Lancet.* 1999;353:2001-2007. [8]SENIORS Study Group. *Eur Heart J.* 2005; 26:215-225.
[9]The Xamoterol in Severe heart Failure Study Group. *Lancet.* 1990;336:1-6.

COMET: Effect Carvedilol vs Metoprolol Tartrate on Mortality in HF



Metoprolol tartrate mean dose: 85 mg QD; Carvedilol mean dose: 42 mg QD.
COMET did not evaluate metoprolol succinate, the agent used in the MERIT-HF Trial

Poole-Wilson PA, et al. *Lancet.* 2003;362:7-13.

Beta Blocker Therapy in Heart Failure

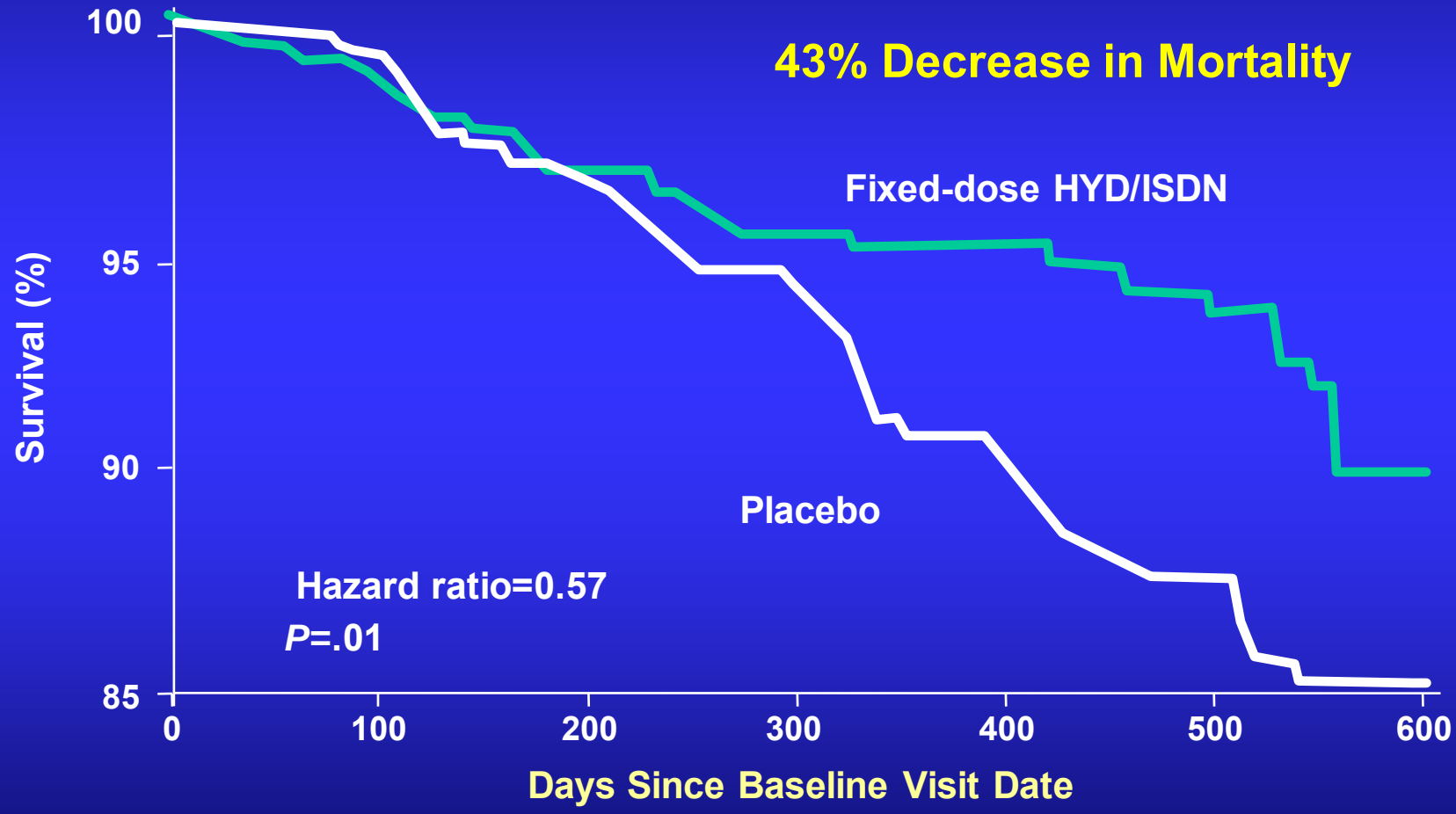
- Indicated for all patients with asymptomatic LVD dysfunction and for Class I to IV Heart Failure with LVEF $\leq$ 0.40
- Contraindications: cardiogenic shock, severe reactive airway disease, 2/3rd degree HB
- Use one the 3 evidence-based beta blockers in HF: eg carvedilol, metroprolol succinate, bisoprolol
- Start at very low HF doses and up-titrate to target doses at two week intervals, or highest dose short of target dose that is well tolerated
- Monitor HR and BP

Yancy CW et al. *J Am Coll Cardiol.* 2013.

Drugs Commonly Used for HF*r*EF (Stage C HF) (cont.)

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials
Beta Blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d (118)
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d (446)
Carvedilol CR	10 mg once	80 mg once	---------
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once	159 mg/d (447)
Hydralazine & Isosorbide Dinitrate			
Fixed dose combination (423)	37.5 mg hydralazine/ 20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/ 40 mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate (448)	Hydralazine: 25 to 50 mg, 3 or 4 times daily and isorsorbide dinitrate: 20 to 30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses	---------

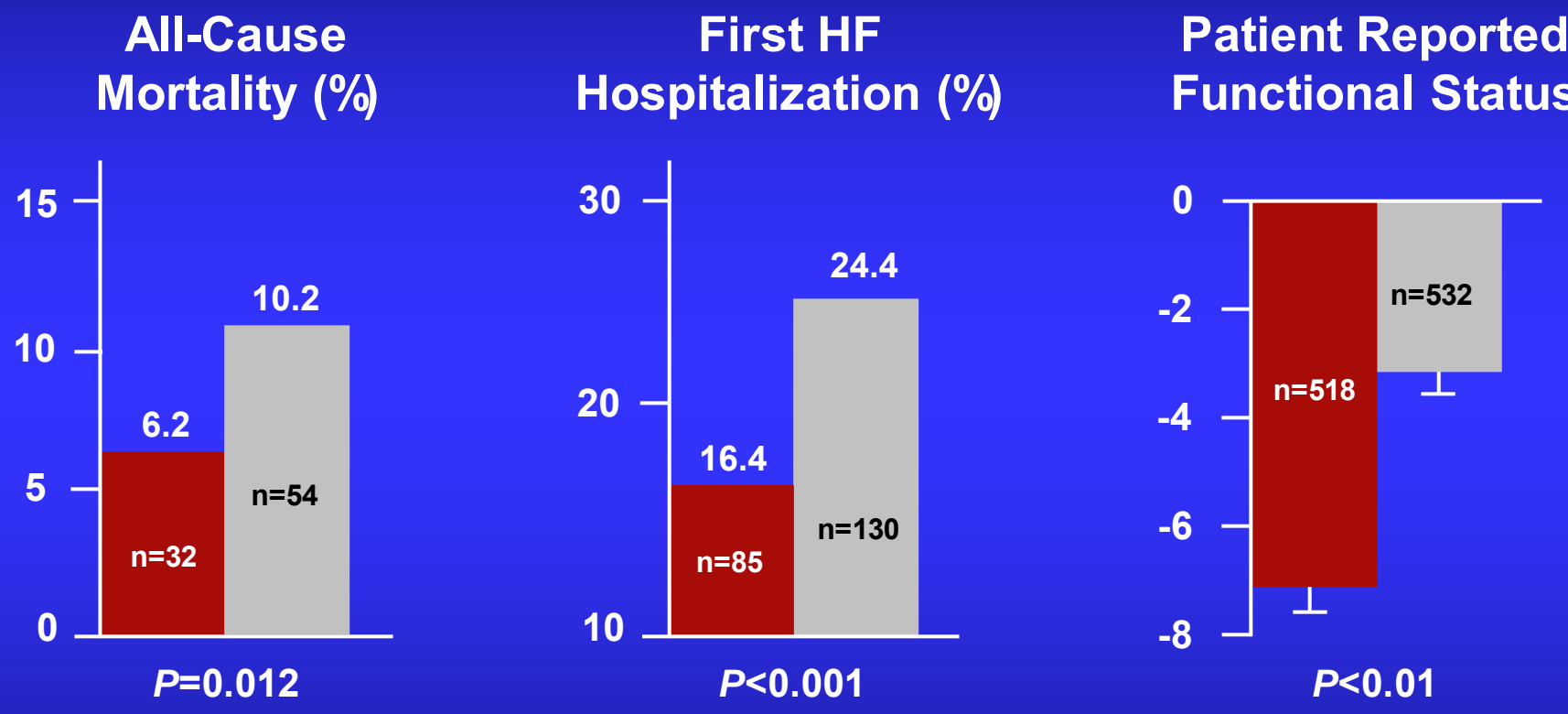
AHeFT: Trial Summary



1050 African Americans with Class III to IV HF, LVEF 24%, on ACEI, BB, AA

Adapted from Taylor AL, et al. *N Engl J Med.* 2004;351:2052.

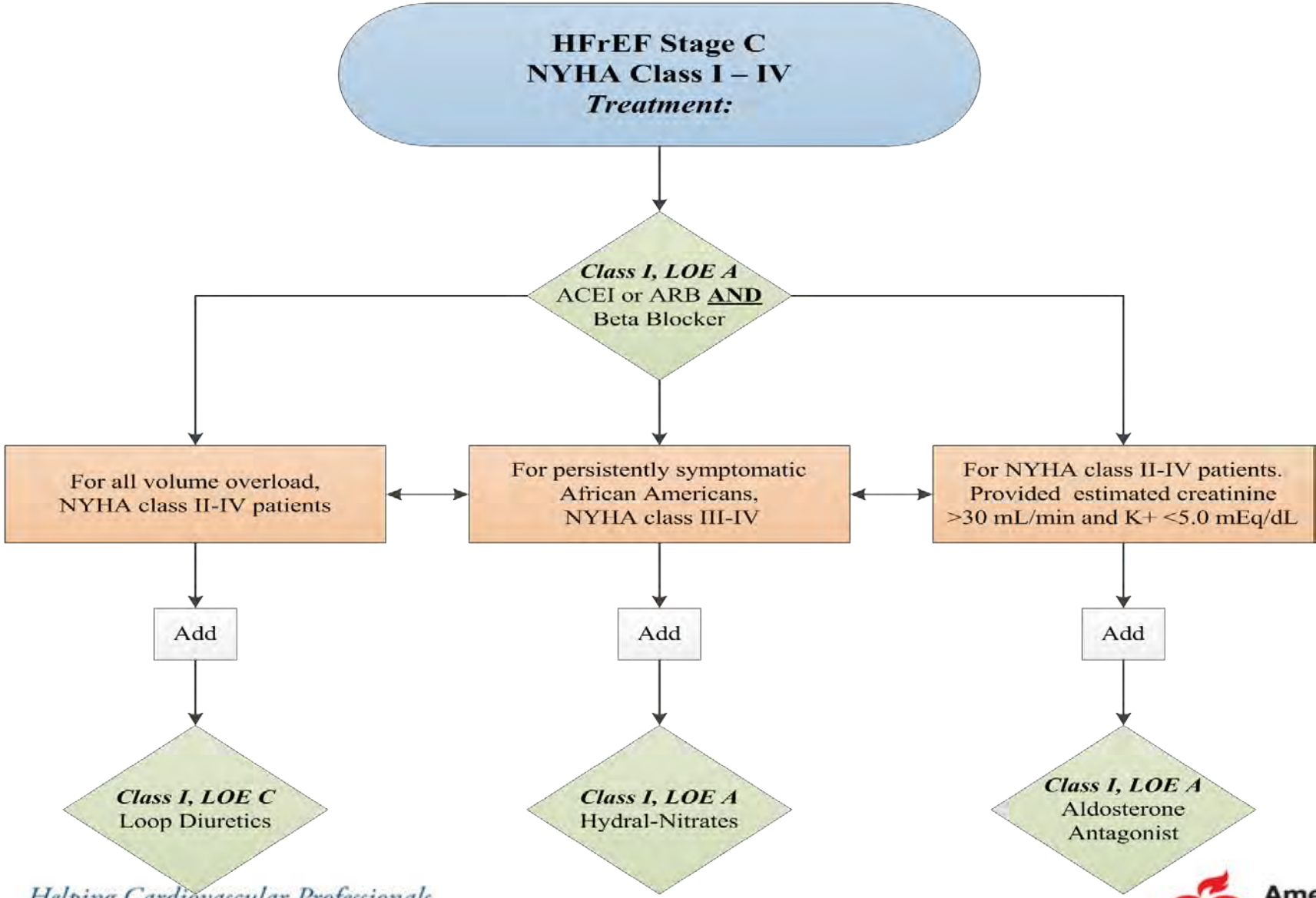
AHeFT: Trial Summary



1050 African Americans with Class III to IV HF, LVEF 24%, on ACEI, BB, AA

Adapted from Taylor AL, et al. *N Engl J Med.* 2004;351:2052.

Pharmacologic Treatment for Stage C HF*r*EF



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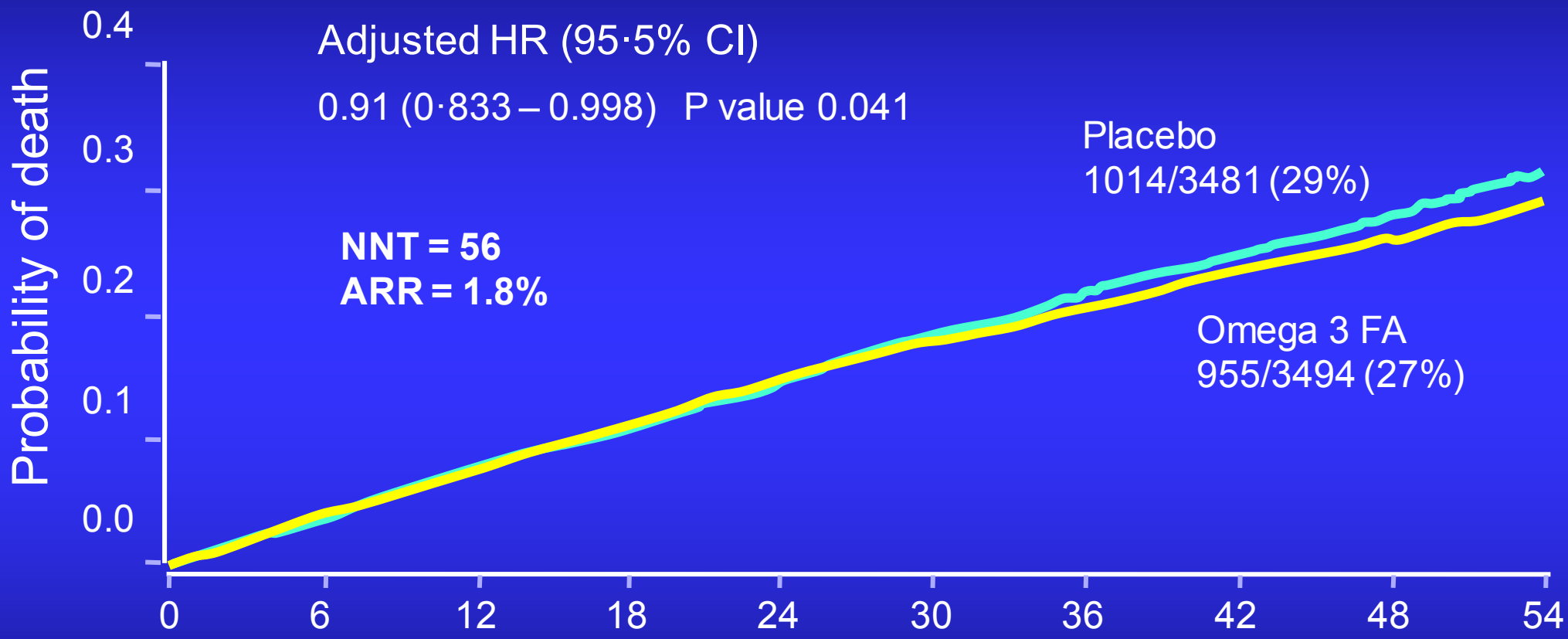
GISSI HF: *All-cause Mortality*



Patients at risk

Omega 3FA	3,494	3,336	3,215	3,080	2,947	2,844	2,680	2,164	1,588	844
Placebo	3,481	3,344	3,209	3,083	2,941	2,805	2,631	2,122	1,558	816

HR = hazard ratio; CI=confidence interval; NNT=number needed to treat; ARR=absolute risk reduction

GISSI-HF Investigators. *Lancet*. In Press.

Pharmacological Therapy for Management of Stage C HF*r*EF

Recommendations	COR	LOE
Diuretics		
Diuretics are recommended in patients with HFrEF with fluid retention	I	C
ACE Inhibitors		
ACE inhibitors are recommended for all patients with HFrEF	I	A
ARBs		
ARBs are recommended in patients with HFrEF who are ACE inhibitor intolerant	I	A
ARBs are reasonable as alternatives to ACE inhibitor as first line therapy in HFrEF	IIa	A
The addition of an ARB may be considered in persistently symptomatic patients with HFrEF on GDMT	IIb	A
Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful	III: Harm	C

Pharmacological Therapy for Management of Stage C HF*r*EF (cont.)

Recommendations	COR	LOE
Beta Blockers		
Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients	I	A
Aldosterone Antagonists		
Aldosterone receptor antagonists are recommended in patients with NYHA class II-IV HF who have LVEF ≤35%	I	A
Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF ≤40% with symptoms of HF or DM	I	B
Inappropriate use of aldosterone receptor antagonists may be harmful	III: Harm	B
Hydralazine and Isosorbide Dinitrate		
The combination of hydralazine and isosorbide dinitrate is recommended for African-Americans, with NYHA class III–IV HFrEF on GDMT	I	A
A combination of hydralazine and isosorbide dinitrate can be useful in patients with HFrEF who cannot be given ACE inhibitors or ARBs	IIa	B

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Pharmacologic Therapy for Management of Stage C HF*r*EF (cont.)

Recommendations	COR	LOE
Digoxin		
Digoxin can be beneficial in patients with HFrEF	IIa	B
Anticoagulation		
Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy*	I	A
The selection of an anticoagulant agent should be individualized	I	C
Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but without an additional risk factor for cardioembolic stroke*	IIa	B
Anticoagulation is not recommended in patients with chronic HFrEF without AF, prior thromboembolic event, or a cardioembolic source	III: No Benefit	B
Statins		
Statins are not beneficial as adjunctive therapy when prescribed solely for HF	III: No Benefit	A
Omega-3 Fatty Acids		
Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in HFrEF or HFpEF patients	IIa	B

Pharmacological Therapy for Management of Stage C HF*r*EF (cont.)

Recommendations	COR	LOE
Other Drugs		
Nutritional supplements as treatment for HF are not recommended in HFrEF	III: No Benefit	B
Hormonal therapies other than to replete deficiencies are not recommended in HFrEF	III: No Benefit	C
Drugs known to adversely affect the clinical status of patients with HFrEF are potentially harmful and should be avoided or withdrawn	III: Harm	B
Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation	III: Harm	C
Calcium Channel Blockers		
Calcium channel blocking drugs are not recommended as routine in HFrEF	III: No Benefit	A

Cardiac Resynchronization Therapy for Heart Failure

- In patients with heart failure 27 to 53% of patients have IVCDs (RBBB, LBBB, IVCD)
- Abnormal conduction contributes to abnormal ventricular activation/contraction and subsequent dysynchrony between the RV and LV
  - Reduced systolic performance
  - Mechanical inefficiency
  - Worsened prognosis

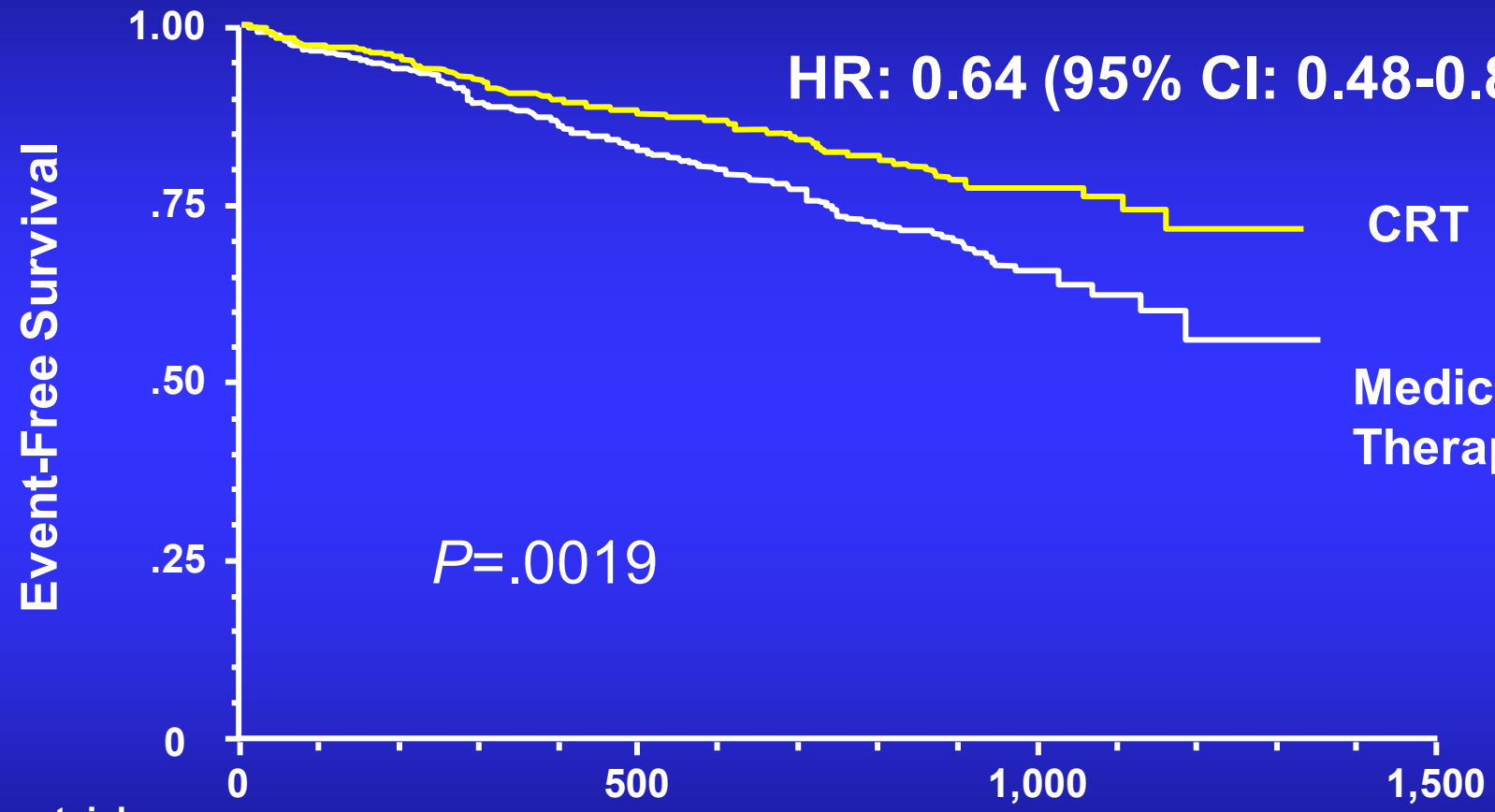
Aarronson Circulation 1997;96. Grines Circulation 1989;79
Xiao Int J Cardiol 1996;53

Cardiac Resynchronization Therapy: Weight of Evidence

- >8,000 patients evaluated in randomized controlled trials
- Consistent improvement in quality of life, functional status, and exercise capacity
- Strong evidence of reverse remodeling
  - ↓ LV volumes and dimensions
  - ↑ LVEF
  - ↓ Mitral regurgitation
- Reduction in HF and all-cause morbidity and mortality

Updated from Abraham WT. *Circulation*. 2003;108:2596-2603.

CARE-HF: Effect of CRT Without an ICD on All-Cause Mortality



Number at risk						
CRT plus meds	409	376	351	213	89	8
Medical Rx	404	365	321	192	71	5

Cleland JG, et al. *N Engl J Med*. 2005:352;1539-1549.

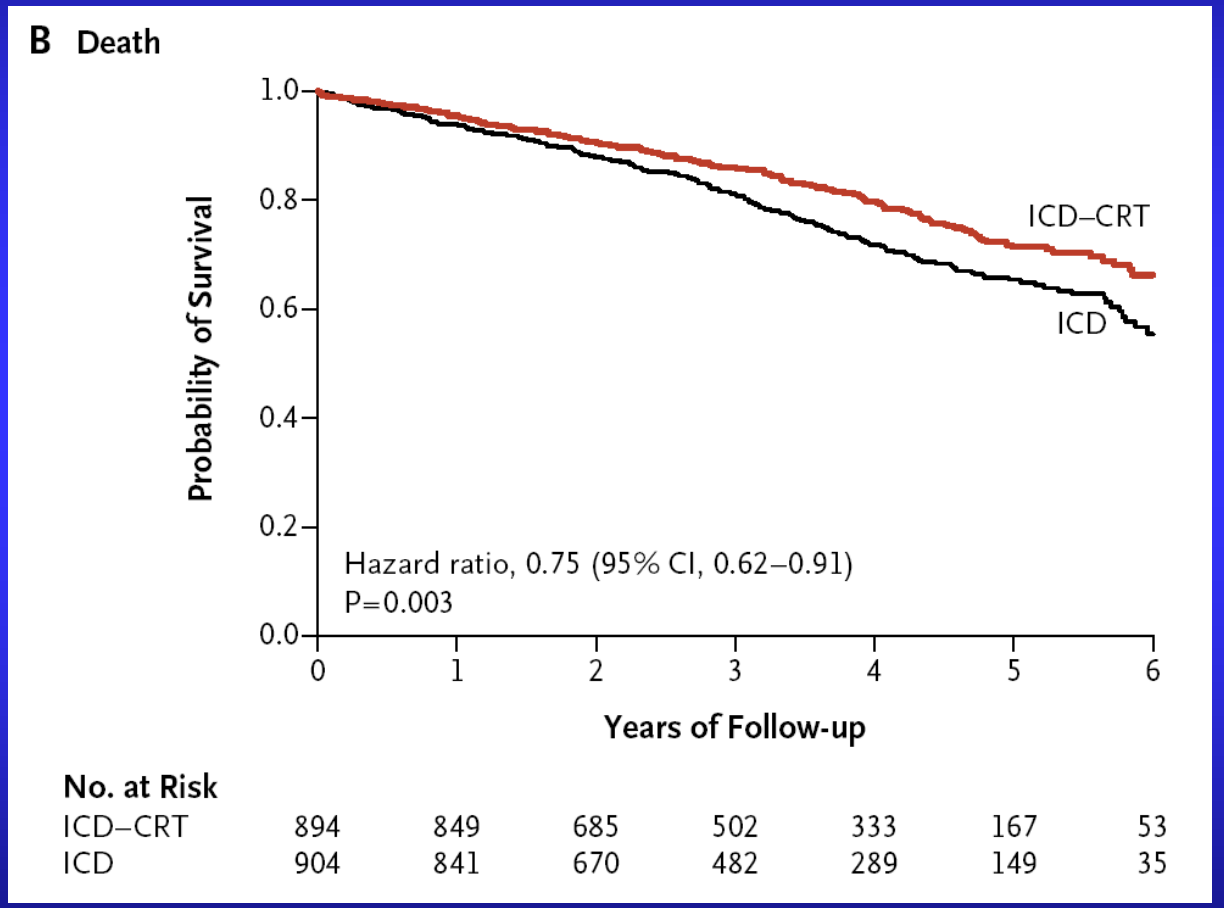
CARE-HF: Clinical Outcomes

	OMT (n=404)	CRT + OMT (n=409)	Hazard Ratio (95% CI)	*P* Value
Death + CV Hospitalization	225 (55%)	159 (39%)	.63 (.51 to .77)	<.001
CV Hospitalization	184 (46%)	125 (31%)	0.61 (.49 to .77)	<.001
HF Hospitalization	133 (33%)	72 (18%)	0.48 (.36 to .64)	<.001
All-Cause Death	120 (30%)	82 (20%)	0.64 (.48 to .85)	<.002

OMT=optimal medical therapy.

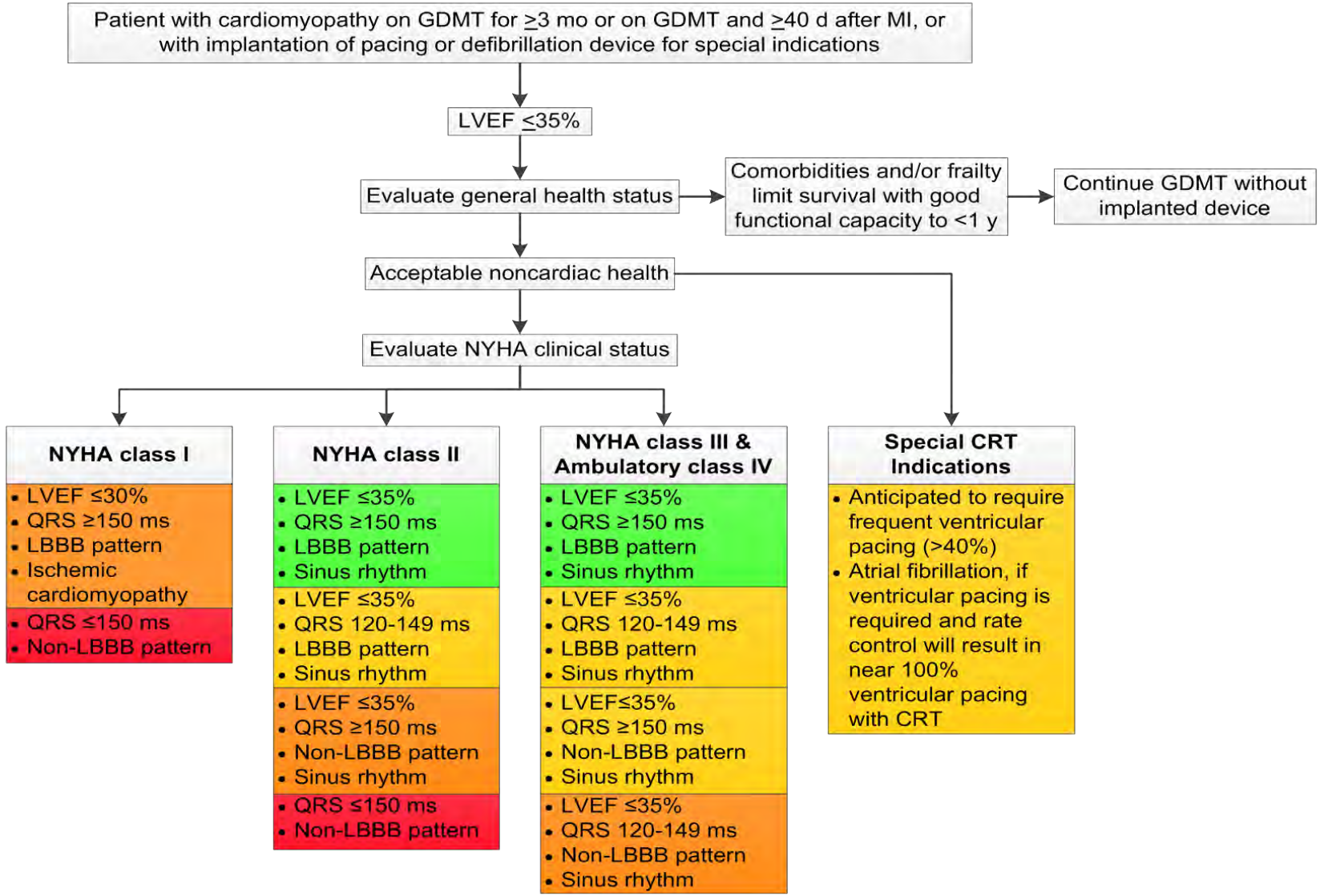
Cleland JG et al. *N Engl J Med*. 2005;352:1539-1549.

Effect of CRT on Mortality in Patients with NYHA Class II HF



1798 Patients is LVEF ≤ 30%, QRS duration 120 ms or above and NYHA Class II on optimal medical therapy RAFT NEJM 2009, online

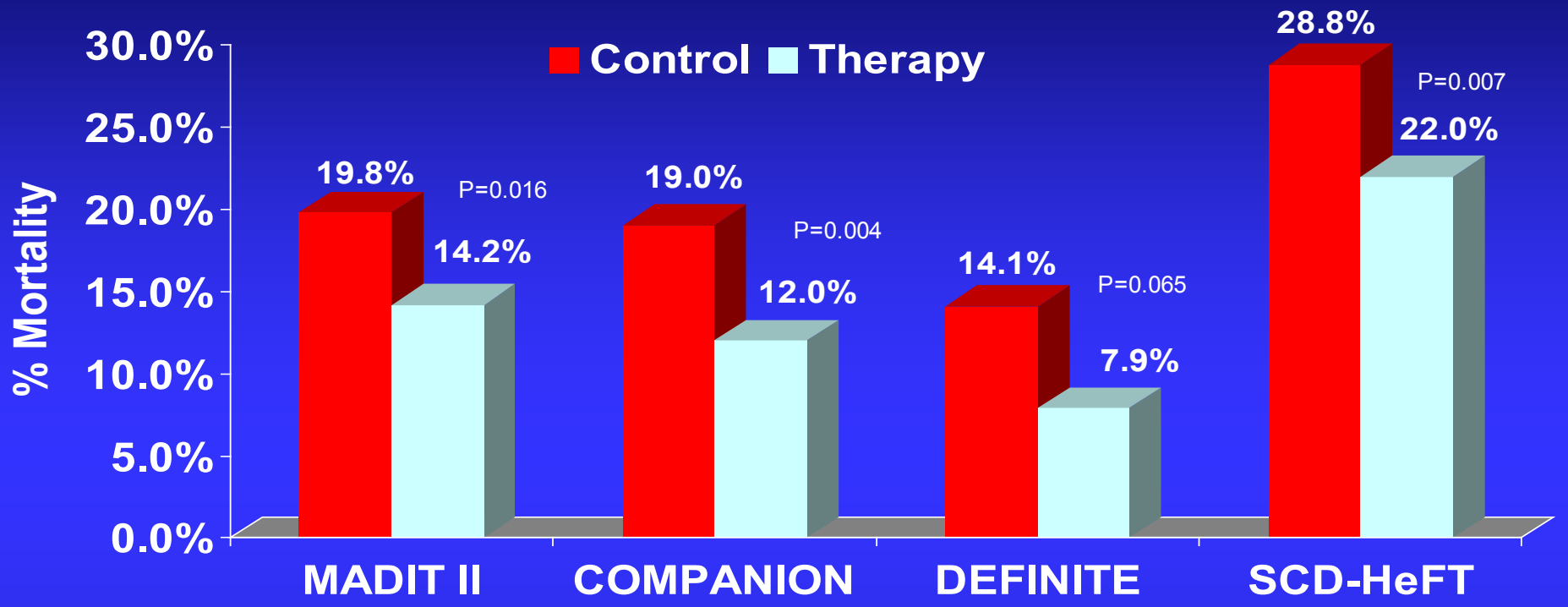
Indications for CRT Therapy



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.

SCD-HeFT and Other ICD Device Trials in HF



HF Etiology	Ischemic: 100%	Ischemic:59% Non-ischemic:41%	Non-ischemic: 100%	Ischemic: 52% Non-ischemic:48%
NYHA Class	I/II/III (35%/35%/30%)	III/IV (87%/13%)	I/II/III (20%/60%/20%)	II/III (71%/29%)
LVEF	≤ 30%	≤ 35%	≤ 35%	≤ 35%
No. Pts	1232	1520	458	2521
Follow-Up	20 months	12 months	24 months	45 months
Hazard Ratio	0.69	0.64	0.66	0.77

Device Therapy for Stage C HF*r*EF (cont.)

Recommendations	COR	LOE
ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF ≤35%, and NYHA class II or III symptoms on chronic GDMT, who are expected to live ≥1 year*	I	A
CRT is indicated for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS ≥150 ms	I	A (NYHA class III/IV)
		B (NYHA class II)
ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF ≤30%, and NYHA class I symptoms while receiving GDMT, who are expected to live ≥1 year*	I	B
CRT can be useful for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB pattern with a QRS ≥150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT.	IIa	A
CRT can be useful for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS 120 to 149 ms, and NYHA class II, III or ambulatory IV symptoms on GDMT	IIa	B
CRT can be useful in patients with AF and LVEF ≤35% on GDMT if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or rate control allows near 100% ventricular pacing with CRT	IIa	B

Important Comorbidities in Heart Failure

- Cardiovascular
  - Hypertension
  - Coronary artery disease
  - Peripheral vascular disease
  - Cerebral vascular disease
  - Hyperlipidemia
  - Atrial fibrillation
- Non-Cardiovascular
  - Obesity
  - Diabetes
  - Anemia
  - Chronic kidney disease
  - Thyroid disease
  - COPD / Asthma
  - Smoking
  - Sleep disordered breathing
  - Liver disease
  - Arthritis
  - Cancer
  - Depression

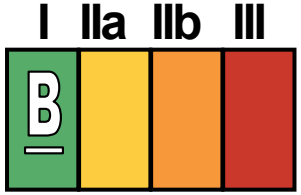
Horwich and Fonarow, Chapter 40: Impact and Treatment of Comorbidities in Heart Failure

ACC/AHA Guidelines for HF Comorbidites and Related Risks

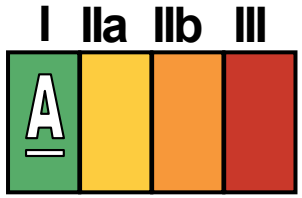
- Control of systolic and diastolic hypertension in accordance with recommended guidelines
  - Appropriate antihypertensive regimen frequently consists of several drugs used in combination
  - Drugs that are useful for the treatment of both hypertension and HF are preferred (eg, ACE inhibitors, β-blockers, aldosterone antagonists, diuretics)
- Treat lipid disorders
- Encourage smoking cessation and regular exercise
- Discourage alcohol intake/illicit drug use

Yancy et al. *J Am Coll Cardiol.* 2013

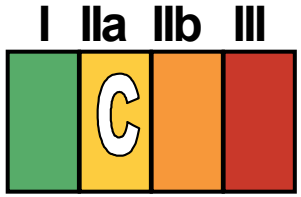
Stage C: Nonpharmacological Interventions



Patients with HF should receive specific education to facilitate HF self-care.

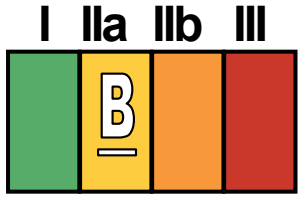


Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status.

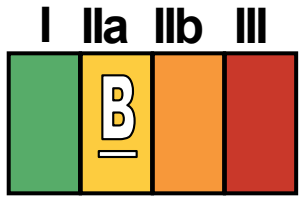


Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms.

Stage C: Nonpharmacological Interventions (cont.)



Continuous positive airway pressure (CPAP) can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea.



Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, HRQOL, and mortality.

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

Therapies in the Hospitalized HF Patient

Recommendation	COR	LOE
HF patients hospitalized with fluid overload should be treated with intravenous diuretics	I	B
HF patients receiving loop diuretic therapy, should receive an initial parenteral dose greater than or equal to their chronic oral daily dose, then should be serially adjusted	I	B
HFrEF patients requiring HF hospitalization on GDMT should continue GDMT unless hemodynamic instability or contraindications	I	B
Initiation of beta-blocker therapy at a low dose is recommended after optimization of volume status and discontinuation of intravenous agents	I	B
Thrombosis/thromboembolism prophylaxis is recommended for patients hospitalized with HF	I	B
Serum electrolytes, urea nitrogen, and creatinine should be measured during the titration of HF medications, including diuretics	I	C

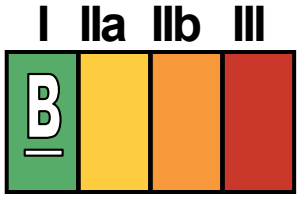
Therapies in the Hospitalized HF Patient (cont.)

Recommendation	COR	LOE
When diuresis is inadequate, it is reasonable to a) Give higher doses of intravenous loop diuretics; or b) add a second diuretic (e.g., thiazide)	IIa	B B
Low-dose dopamine infusion may be considered with loop diuretics to improve diuresis	IIb	B
Ultrafiltration may be considered for patients with obvious volume overload	IIb	B
Ultrafiltration may be considered for patients with refractory congestion	IIb	C
Intravenous nitroglycerin, nitroprusside or nesiritide may be considered an adjuvant to diuretic therapy for stable patients with HF	IIb	B
In patients hospitalized with volume overload and severe hyponatremia, vasopressin antagonists may be considered	IIb	B

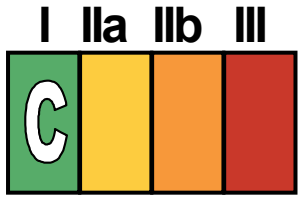
Hospital Discharge

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

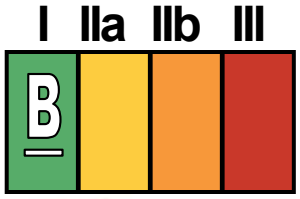
Coordinating Care for Patients With Chronic HF



Effective systems of care coordination with special attention to care transitions should be deployed for every patient with chronic HF that facilitate and ensure effective care that is designed to achieve GDMT and prevent hospitalization.



Every patient with HF should have a clear, detailed and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with Secondary Prevention Guidelines for cardiovascular disease. This plan of care should be updated regularly and made readily available to all members of each patient's healthcare team.



Palliative and supportive care is effective for patients with symptomatic advanced HF to improve quality of life.

Ivabradine and Outcomes in Chronic Heart Failure (SHIFT)

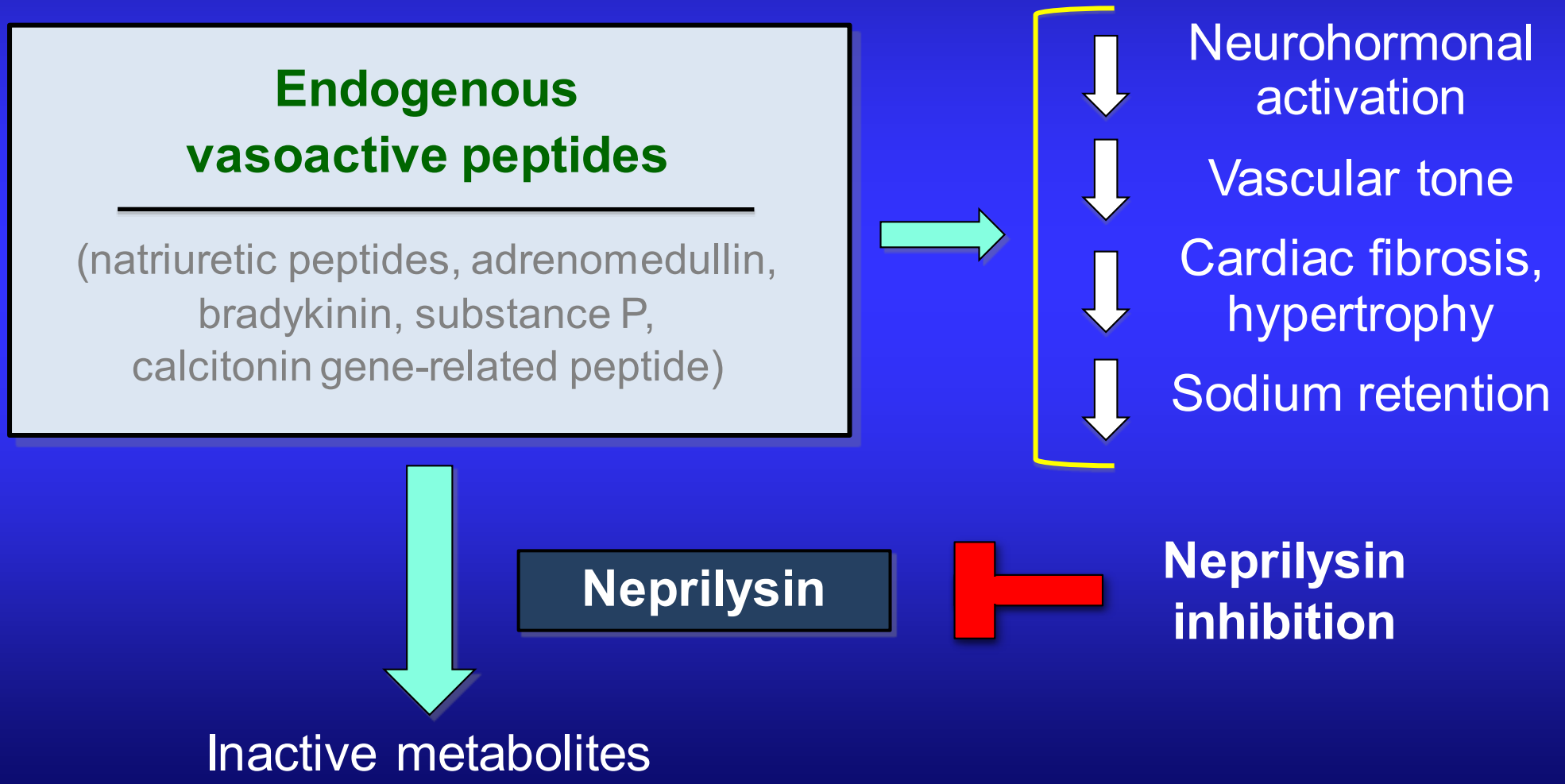
SHIFT: Hazard ratios for primary and individual outcomes, ivabradine vs placebo groups

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

The benefit of ivabradine appeared to go up with increasing heart rate (HR<77 HR 0.93; HR≥77 HR 0.75)

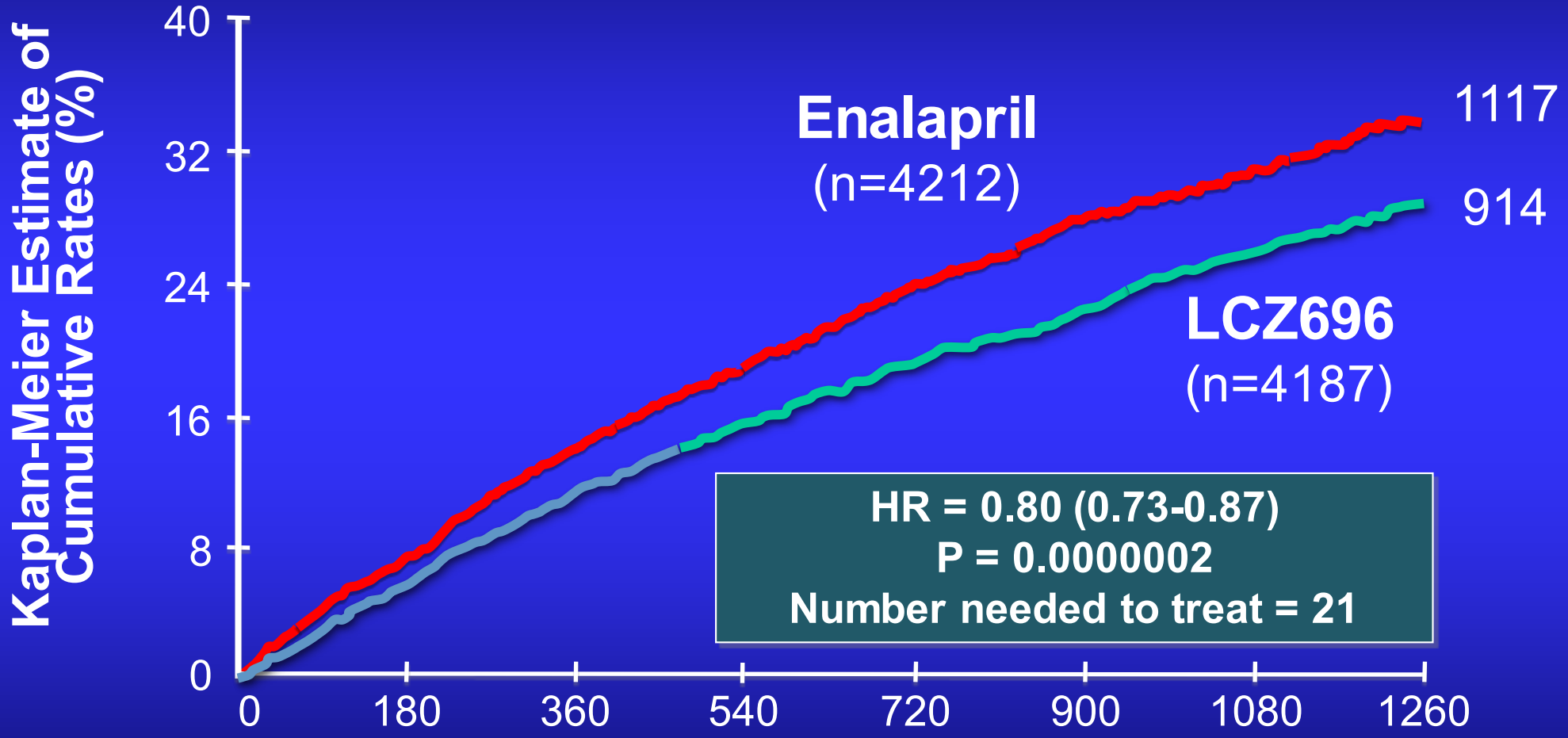
6558 patients with LVEF ≤35%, Sinus rhythm ≥70 bpm
Swedberg et al. Lancet 2010

Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure



McMurray JJ et al. N Engl J Med. 2014 Sep 11;371(11):993-1004.

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



Patients at Risk

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

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

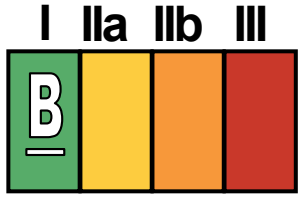
McMurray JJ et al. N Engl J Med. 2014 Sep 11;371(11):993-1004.

Evidence-Based, Guideline-Recommended Heart Failure with Reduced EF Therapies

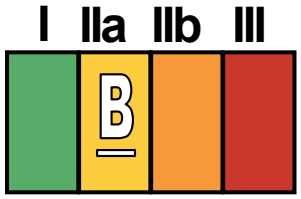
Guideline Recommended Therapy	Relative Risk Reduction in Mortality	Number Needed to Treat for Mortality	NNT for Mortality (standardized to 36 months)	Relative Risk Reduction in HF Hospitalizations
ACEI/ARB	17%	22 over 42 months	26	31%
Beta-blocker	34%	28 over 12 months	9	41%
Aldosterone Antagonist	30%	9 over 24 months	6	35%
Hydralazine/Nitrate	43%	25 over 10 months	7	33%
CRT	36%	12 over 24 months	8	52%
ICD	23%	14 over 60 months	23	NA

Fonarow GC, et al. Am Heart J 2011;161:1024-1030.

Quality Metrics/Performance Measures



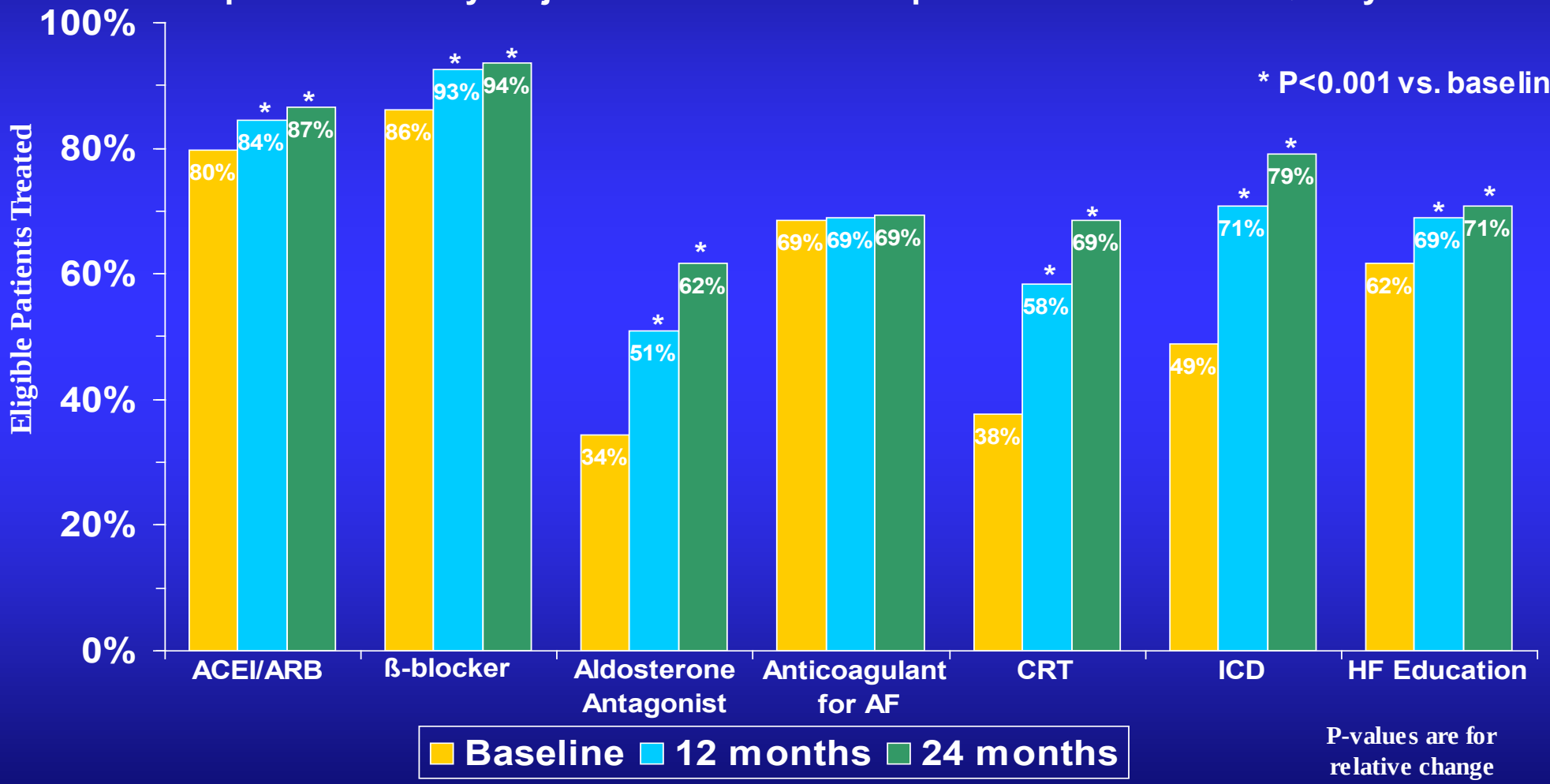
Performance measures based on professionally developed clinical practice guidelines should be used with the goal of improving quality of care for HF.



Participation in quality improvement programs and patient registries based on nationally endorsed, clinical practice guideline-based quality and performance measures may be beneficial in improving quality of HF care.

IMPROVE HF Primary Results: Improvement in Quality Measures at 24 Months (Patient Level Analysis)

Significant Improvement in 6 of 7 Quality Measures at 12 and 24 Months
Pre-specified Primary Objective Met: Relative Improvement ≥ 20% in 3 Quality Measures



Fonarow GC, et al. Circulation. 2010;122:585-596.

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

- Each 10% improvement in ACC/AHA heart failure 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).*

ACC/AHA Guideline Directed Therapy for Heart Failure Improves Outcomes

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

Potential Impact of Optimal Implementation of Evidence-Based HF Therapies on Mortality

Guideline Recommended Therapy	HF Patient Population Eligible for Treatment, n*	Current HF Population Eligible and Untreated, n (%)	Potential Lives Saved per Year	Potential Lives Saved per Year (Sensitivity Range*)
ACEI/ARB	2,459,644	501,767 (20.4)	6516	(3336-11,260)
Beta-blocker	2,512,560	361,809 (14.4)	12,922	(6616-22,329)
Aldosterone Antagonist	603,014	385,326 (63.9)	21,407	(10,960-36,991)
Hydralazine/Nitrate	150,754	139,749 (92.7)	6655	(3407-11,500)
CRT	326,151	199,604 (61.2)	8317	(4258-14,372)
ICD	1,725,732	852,512 (49.4)	12,179	(6236-21,045)
Total	-	-	67,996	(34,813-117,497)

Fonarow GC, et al. Am Heart J 2011;161:1024-1030.

Advances in the Treatment of HF

- Increased attention to prevention
- ACEI / β-blocker / aldosterone antagonist combination established as the "cornerstone" of therapy
- Evidence that β-blockers' effects are not homogeneous
- Downgrade in recommendation for use of digoxin
- Integration of CRT and ICD device therapy into the standard therapeutic regimen
- Recognition that "special populations" of HF patients may benefit from or require different approaches
- New strategies to improve utilization of evidence based therapies

Yancy CW et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Conclusions

- Evidence-based guideline directed diagnosis, evaluation and therapy should be the mainstay for all patients with HF.
- 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: prevention, nonpharmacological therapy of HF including dietary adjustments, treatment of HF*p*EF, management of hospitalized HF, effective reduction in HF readmissions, more precise use of device-based therapy, smaller MCS platforms and cell-based regenerative therapy.