Heart Failure
Update

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Disclosures

- Research Support
  - Federal: NIH, European Union, PCORI
  - Industry: Multiple clinical trials
- Consultant
  - Adrenomed, Amgen, Array, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squib, CVRx, G3 Pharmacautical, Innolife, Janssen, LinaNova, Luitpold, Medtronic, Merck, Novartis, Relypsa, Roche, Sanofi, Vifor

Objectives

- Outline the epidemiology and economic impact of HF
- Incorporate evidence-based therapies to optimize outcomes in patients with HF, including new guideline-recommended therapies
- Recognize the importance of continuity of care for HF patients transitioning from the inpatient to outpatient setting and implement strategies to prevent readmissions

Scope of Heart Failure

Population Group	Prevalence	Incidence	Mortality	Hospital Discharges	Cost[1]
Total population	5,700,000	870,000	50% at 5 years	1,023,000	$30.7 billion

- HF is a major public health problem resulting in substantial morbidity and mortality
- 23 million people with HF worldwide
- 6–12 million office visits
- Costs: ~$31 billion in 2012 (80% due to hospitalizations) and projected to be ~$70 billion by 2030[1,2]

1. Mozaffarian D, et al. *Circulation*. 2015;131:e29-e322. 2. Heidenreich PA, et al. *Circ Heart Fail*. 2013;6(3):606-619.

Classification of HF

ACCF/AHA Stage		NYHA 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	Same as above
		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 out any physical activity without symptoms of HF or symptoms of HF at rest
D	Refractory HF requiring specialized interventions	IV	Unable to carry out any physical activity without symptoms of HF or symptoms of HF at rest

NYHA = New York Heart Association.

Yancy CW, et al. *Circulation.* 2013;128(16):e240-327.

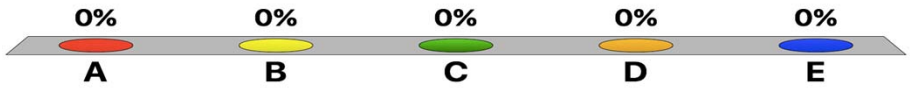
Types of Heart Failure

Classification	Ejection Fraction	Description
I. Heart Failure with Reduced Ejection Fraction (HFrEF)	≤40%	Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart Failure with Preserved Ejection Fraction (HFpEF)	≥50%	Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF 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. HFpEF, Borderline	41% to 49%	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.
b. HFpEF, Improved	≤40%	It has been recognized that a subset of patients with HFpEF previously had HFrEF. 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.

Which of the following therapies for patients with heart failure with reduced ejection fraction have not been shown to reduce mortality?

A. ACE inhibitor
B. Angiotensin receptor neprilysin inhibitor
C. Aldosterone antagonists
✓ D. Ivabradine
E. Beta-blockers



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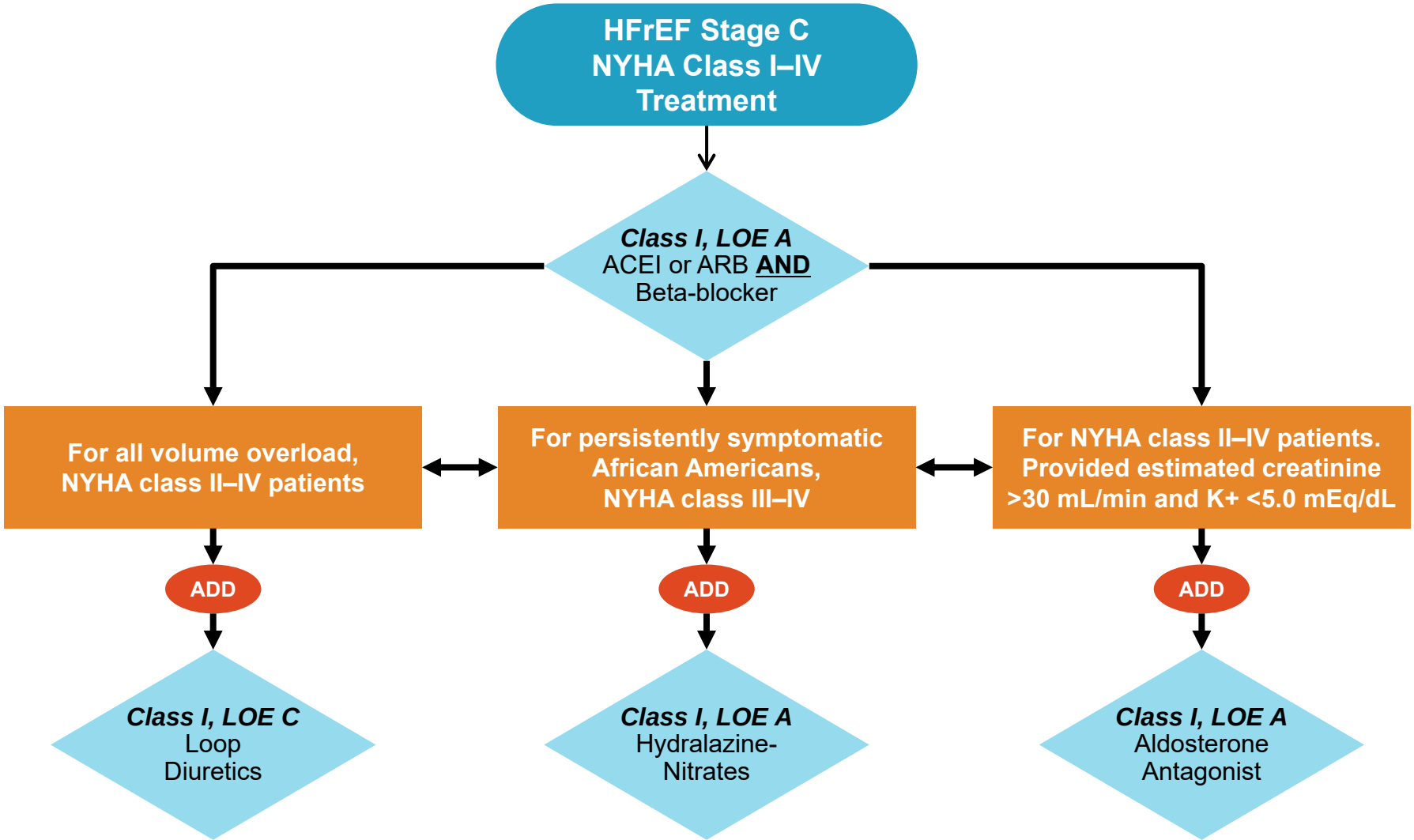
Pharmacologic Treatment for Stage C HFrEF

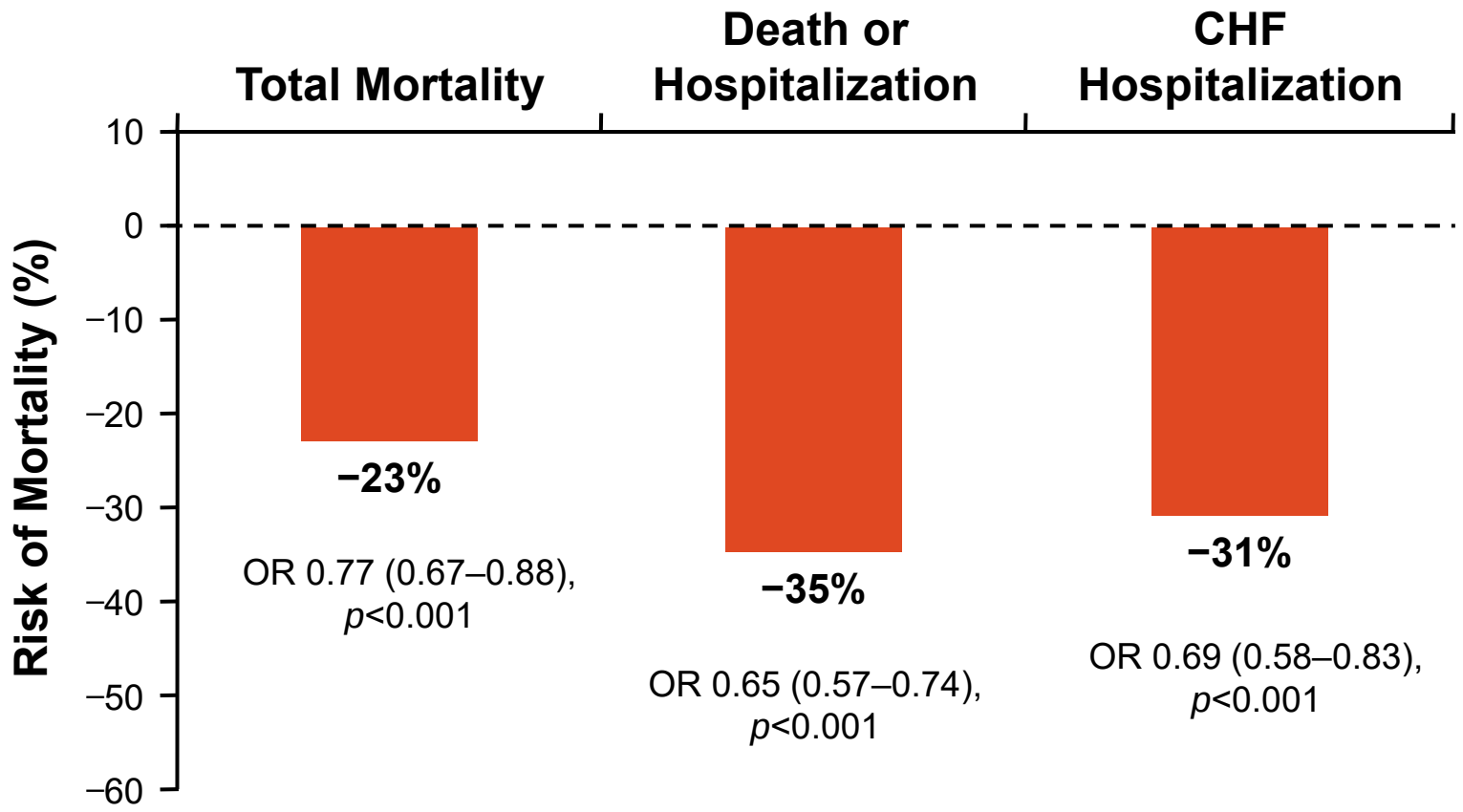


NYHA = New York Heart Association; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; LOE = level of evidence.

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) **vs. Placebo** (n=3235)



OR = odds ratio.

Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273:1450-1456.

High- vs. Low-Dose ACEI Therapy for HF

	Low Dose*	High Dose*	OR	*p*-Value
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 with f/u 46 months, rare use of beta-blockers

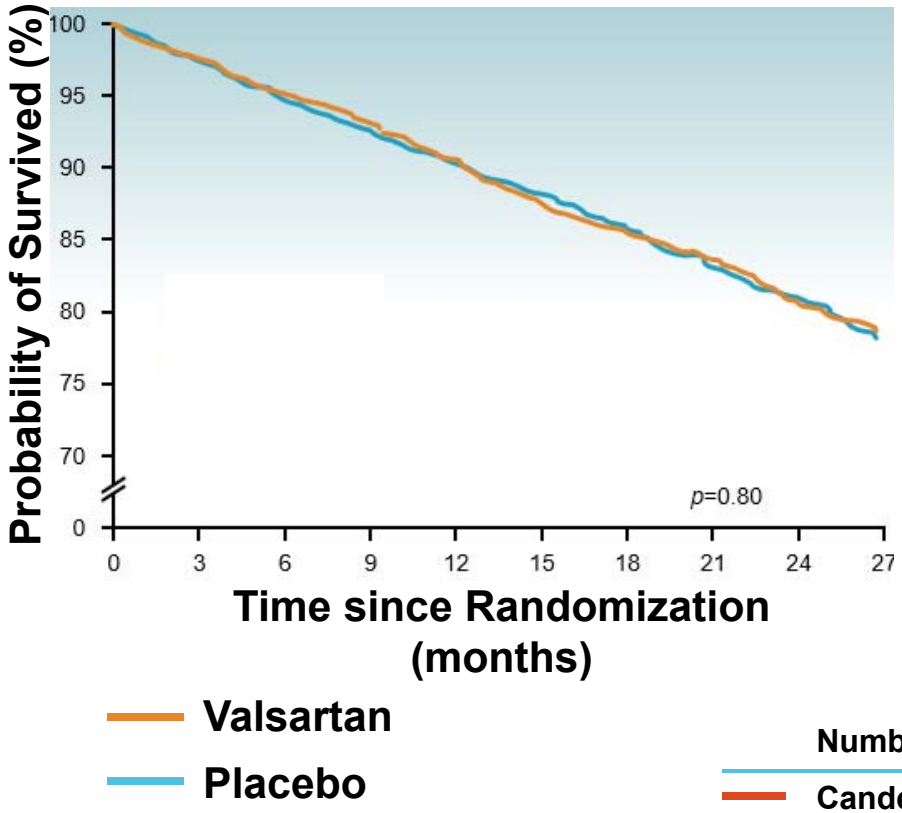
***Low dose = lisinopril 2.5 to 5.0 mg/day, high dose = lisinopril 32.5 to 35.0 mg/day**

f/u = follow-up.

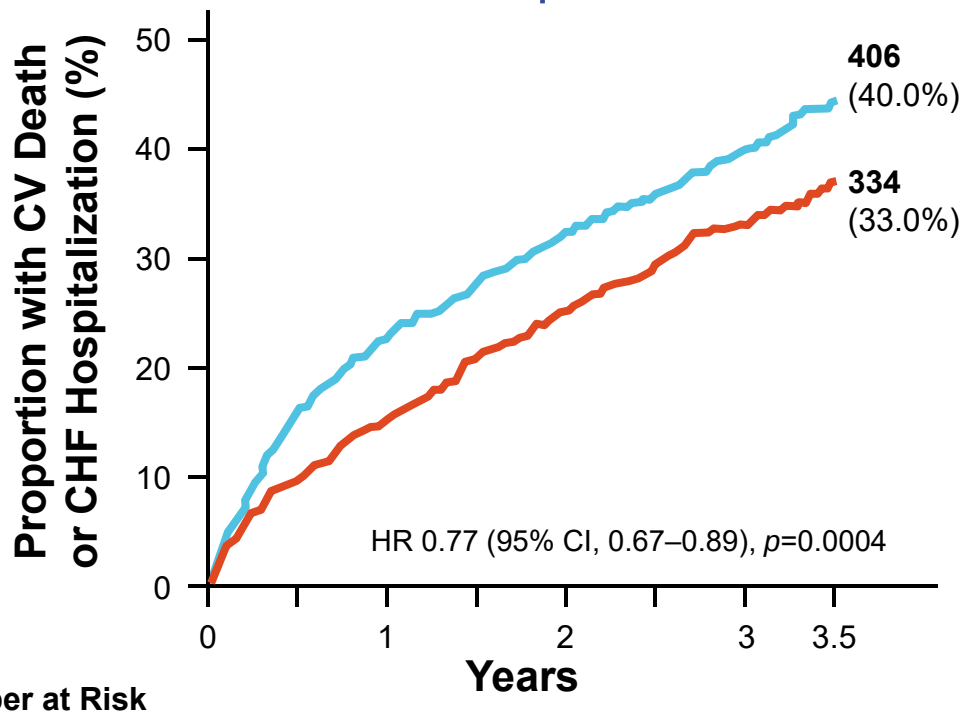
Packer M, et al. *Circulation*. 1999;100:2312-2318.

ARB Added to Standard HF Care

Val-HeFT



CHARM-Alternative
Primary Outcome of CV Death or CHF Hospitalization



Number at Risk					
Candesartan	1013	929	831	434	122
Placebo	1015	887	798	427	126

Val-HeFT = The Valsartan Heart Failure Trial; CHARM = Candesartan in Heart Failure-Assessment of mortality and Morbidity trials; CV = cardiovascular

1. Cohn J, et al. *N Engl J Med*. 2001;345:1667-1675. 2. Granger CB, et al. *Lancet*. 2003;362:772-776. 3. Maggioni AP, et al. *J Am Coll Cardiol*. 2002;40:1414 –21.

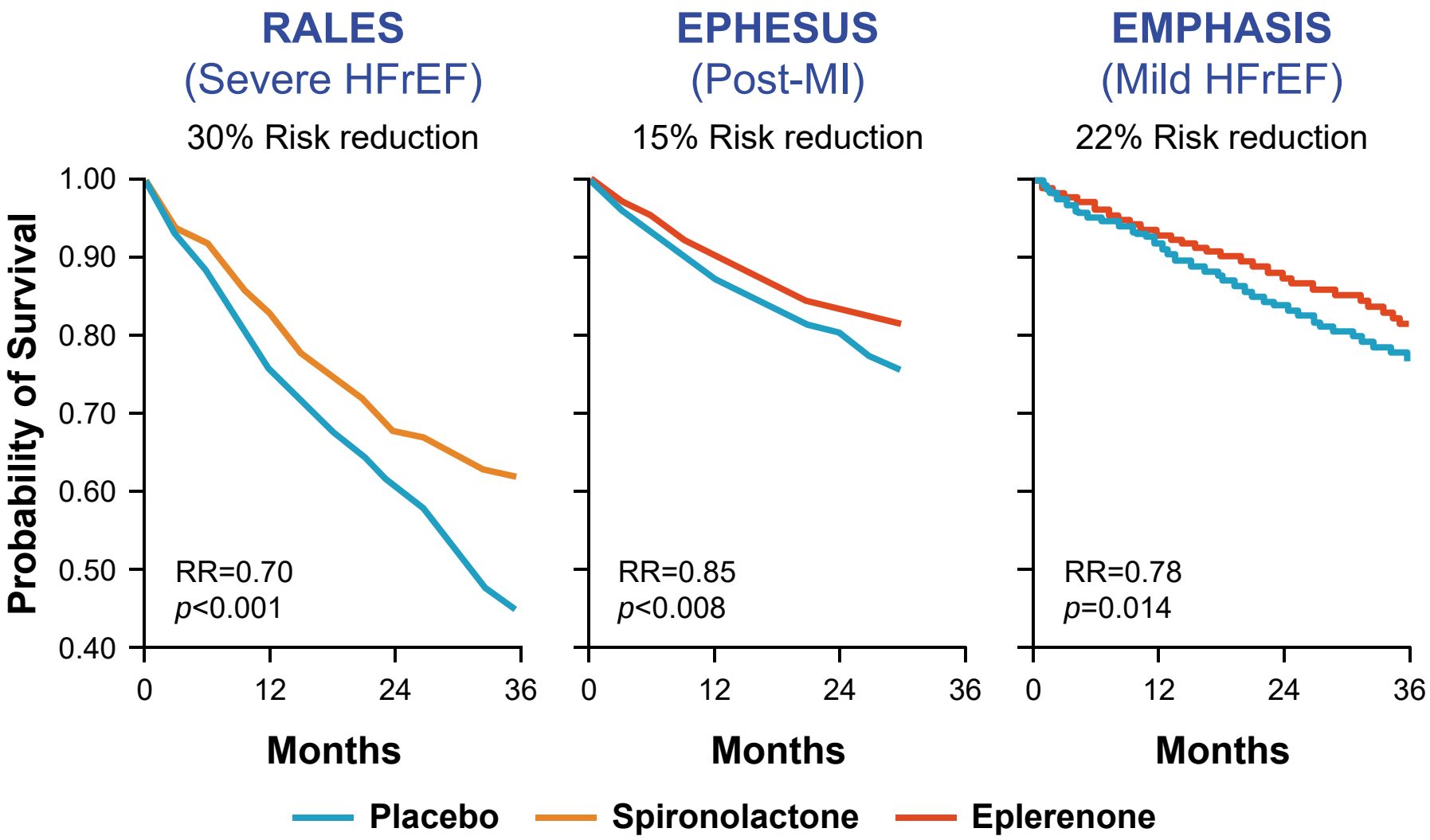
ACEI/ARB in Heart Failure

- Indicated for all patients with asymptomatic LV dysfunction and for class I to IV heart failure (contraindications: hyperkalemia, angioedema, pregnancy)
- Titrate to target doses (i.e., 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
- Use of ACEIs preferred over ARBs
- Use of ACEI together with ARB reserved as a consideration only in patients not candidates for aldosterone antagonist

LV = left ventricular; qd = every day.

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

Aldosterone Antagonists in HF



1. Pitt B, et al. *N Engl J Med*. 1999:341:709-717. 2. Pitt B, et al. *N Engl J Med*. 2003;348:1309-1321. 3. Zannad F, et al. *N Engl J Med*. 2011;364:11-21.

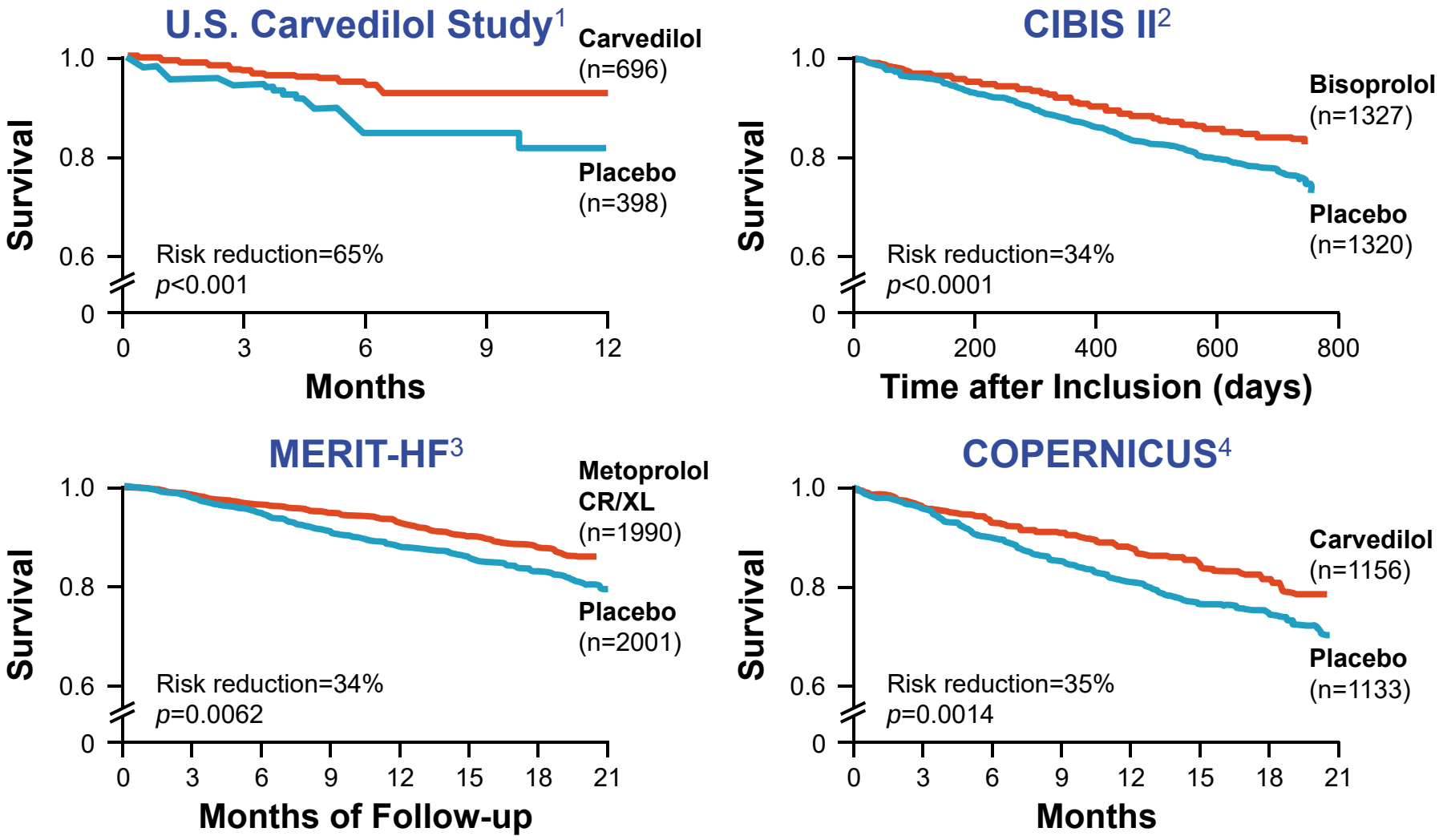
Aldosterone Antagonists in Heart Failure

- Indicated for patients with mild, moderate, or severe HF due to LVD (LVEF ≤0.40)
  - Spironolactone 12.5 mg PO qd starting dose (or 6.25 mg in higher-risk patients) or eplerenone 25 mg PO qd (or 12.5 mg in higher-risk patients)
  - 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 72 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
- Contraindicated if hyperkalemia or Cr >2.5 mg/dL in men and >2.0 mg/dL in women

LVEF = left ventricular ejection fraction; PO = by mouth; Cr = creatinine.

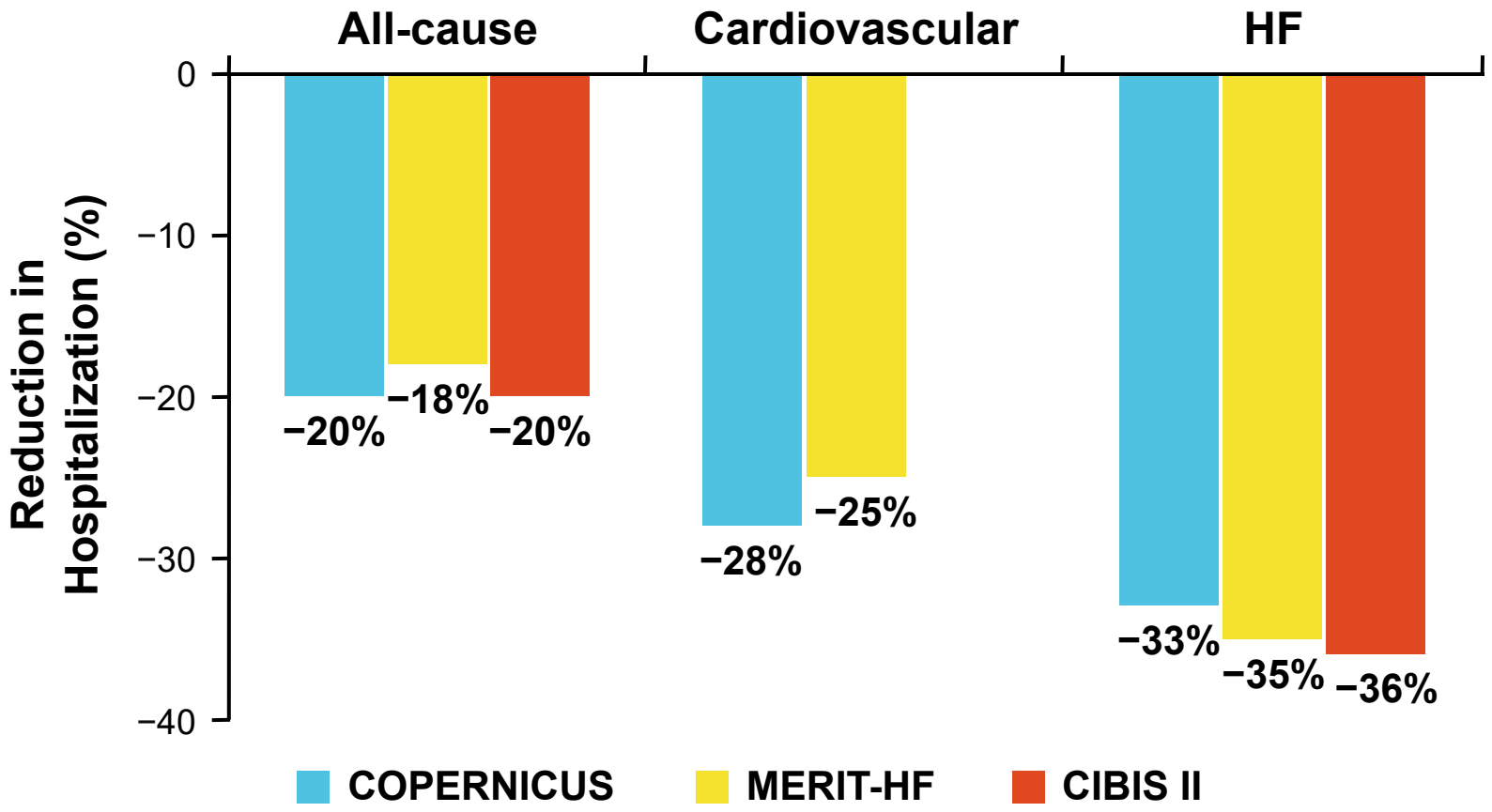
Yancy CW, et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Beta-Blockers in Heart Failure



1. Packer M, et al. *N Engl J Med*. 1996;334:1349-1355. 2. CIBIS II Investigators and Committees. *Lancet*. 1999;353:9-13. 3. MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007. 4. Packer M, et al. *Circulation.* 2002;106(17):2194-9.

Effect of Beta-Blockade on Hospitalizations



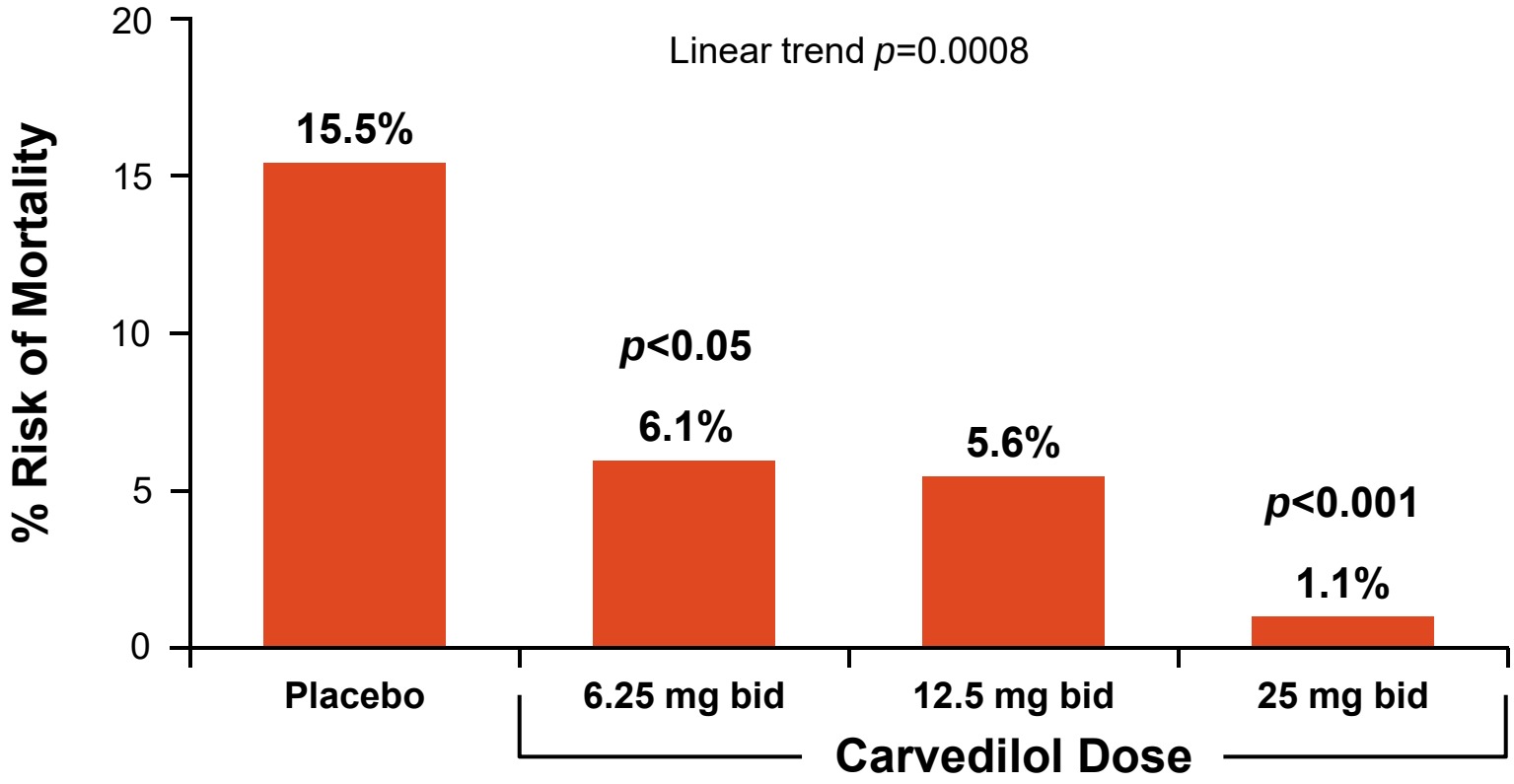
Only carvedilol and metoprolol CR/XL are FDA-approved for HF therapy in the U.S.

FDA = Food and Drug Administration.

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

Carvedilol Dose-Response Trial (MOCHA)



Dose response of carvedilol in moderate HF patients on all-cause mortality

bid = twice daily.

Bristow MR, et al. *Circulation*. 1996;94:2807.

Beta-Blocker Therapy in Heart Failure

- Indicated for all patients with asymptomatic LV dysfunction and for class I to IV HF with LVEF ≤0.40
- Contraindications: cardiogenic shock, severe reactive airway disease, 2/3rd-degree HB
- Use of one of the 3 evidence-based beta-blockers in HF: i.e., 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

HB = heart block; HR = heart rate; BP = blood pressure.

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

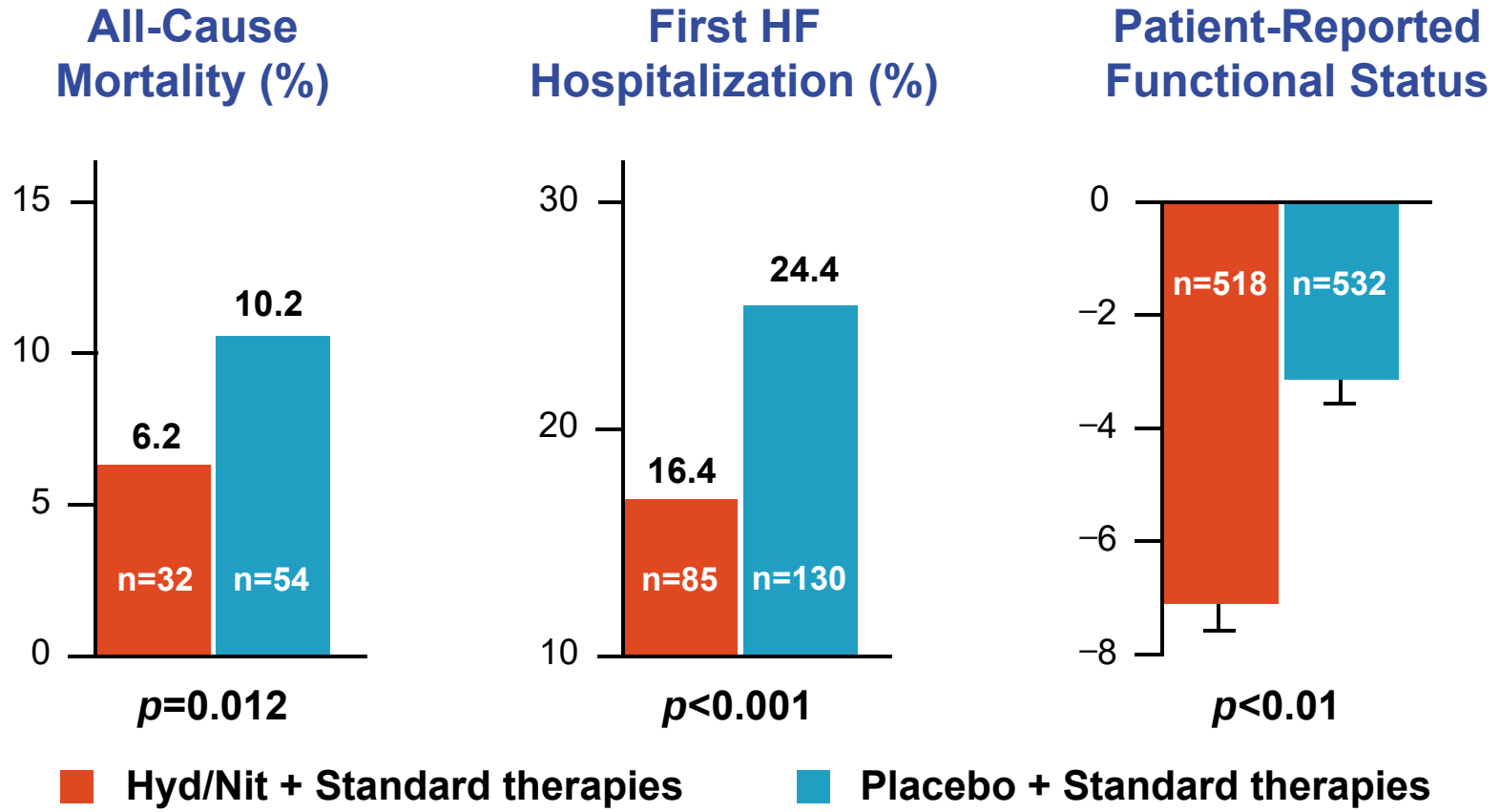
Beta-Blockers Differ in Their Long-Term Effects on Mortality in HF

Beta-Blocker	Long-Term Effect
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.

AHeFT: Trial Summary

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

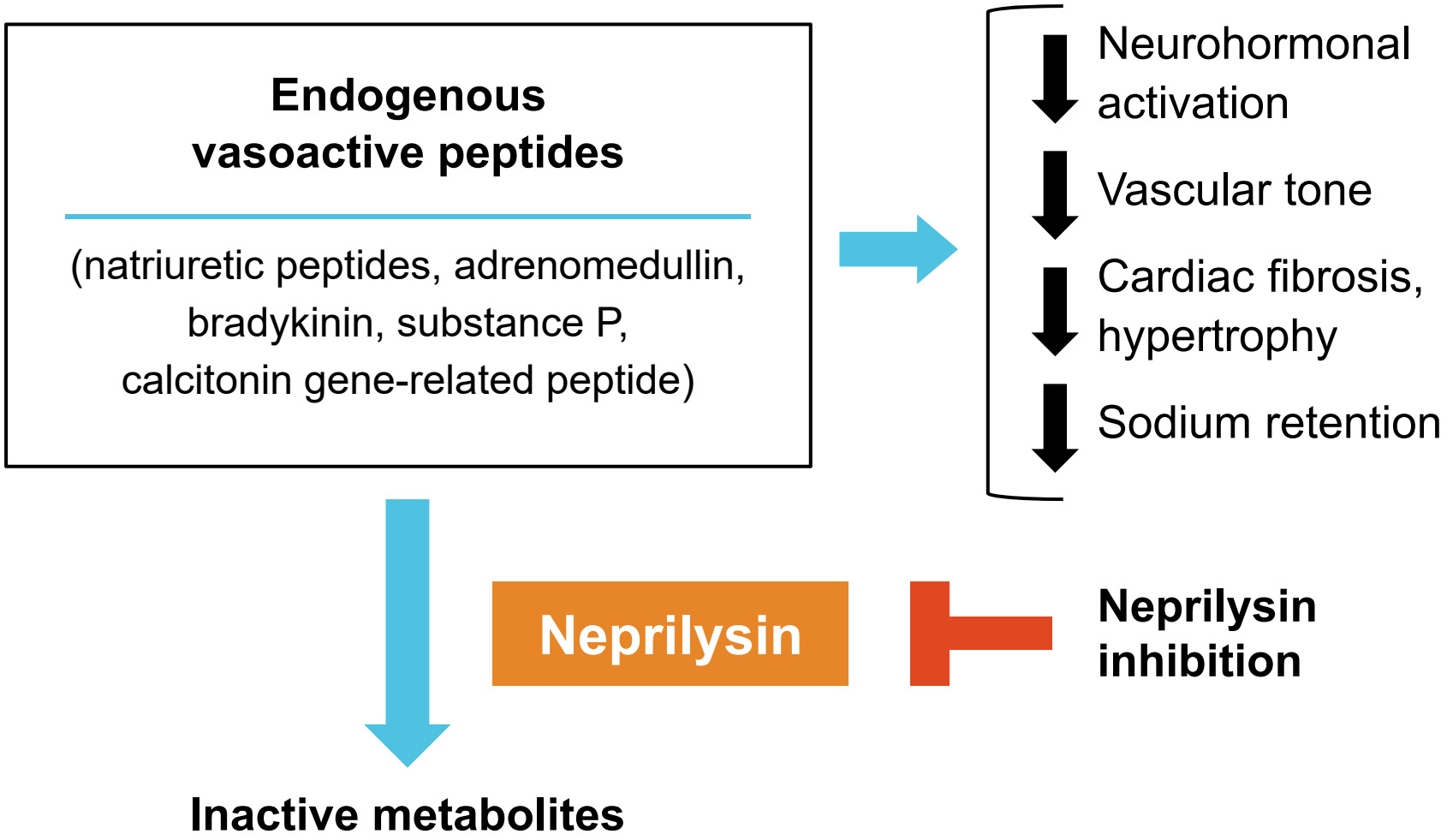


AHeFT = African-American Heart Failure Trial; BB = beta-blocker; AA = aldosterone antagonist; Hyd/Nit = hydralazine/nitrate.

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

Newer Therapies for HFrEF

Effects of Neprilysin Inhibition in Heart Failure

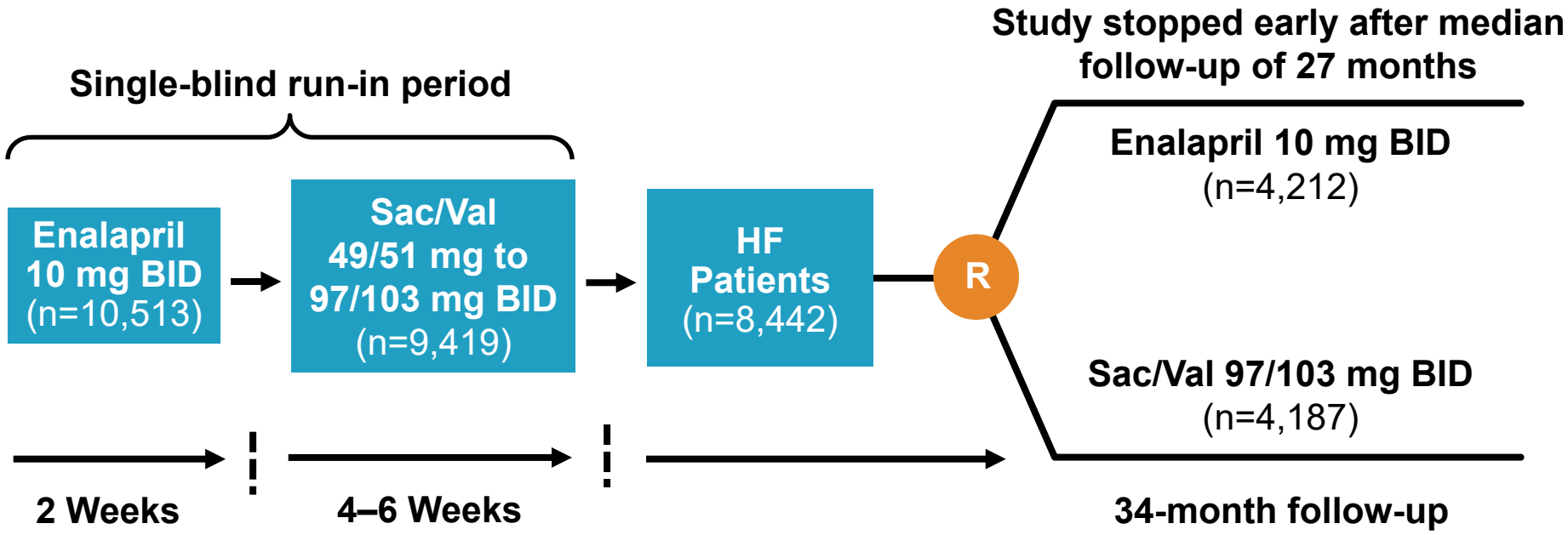


McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004.

PARADIGM-HF Trial: Design

Entry Criteria:

- NYHA class II-IV HF, LVEF ≤40% → amended to ≤35%
- BNP ≥150 pg/mL (or NT-proBNP ≥ 600 pg/mL) or 1/3 lower if hospitalized for HF within 12 months
- On a stable dose of ACEI or ARB equivalent to ≥10 mg of enalapril daily for ≥4 weeks
- Unless contraindicated, on stable dose of beta-blocker for ≥4 weeks
- SBP ≥95 mm Hg, eGFR ≥30 mL/min/1.73 m2 and serum K ≤5.4 mmol/L at randomization



Primary endpoint: Death from CV causes or hospitalization for HF

PARADIGM-HF = Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate; Sac/Val = Sacubitril/Valsartan.

McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004.

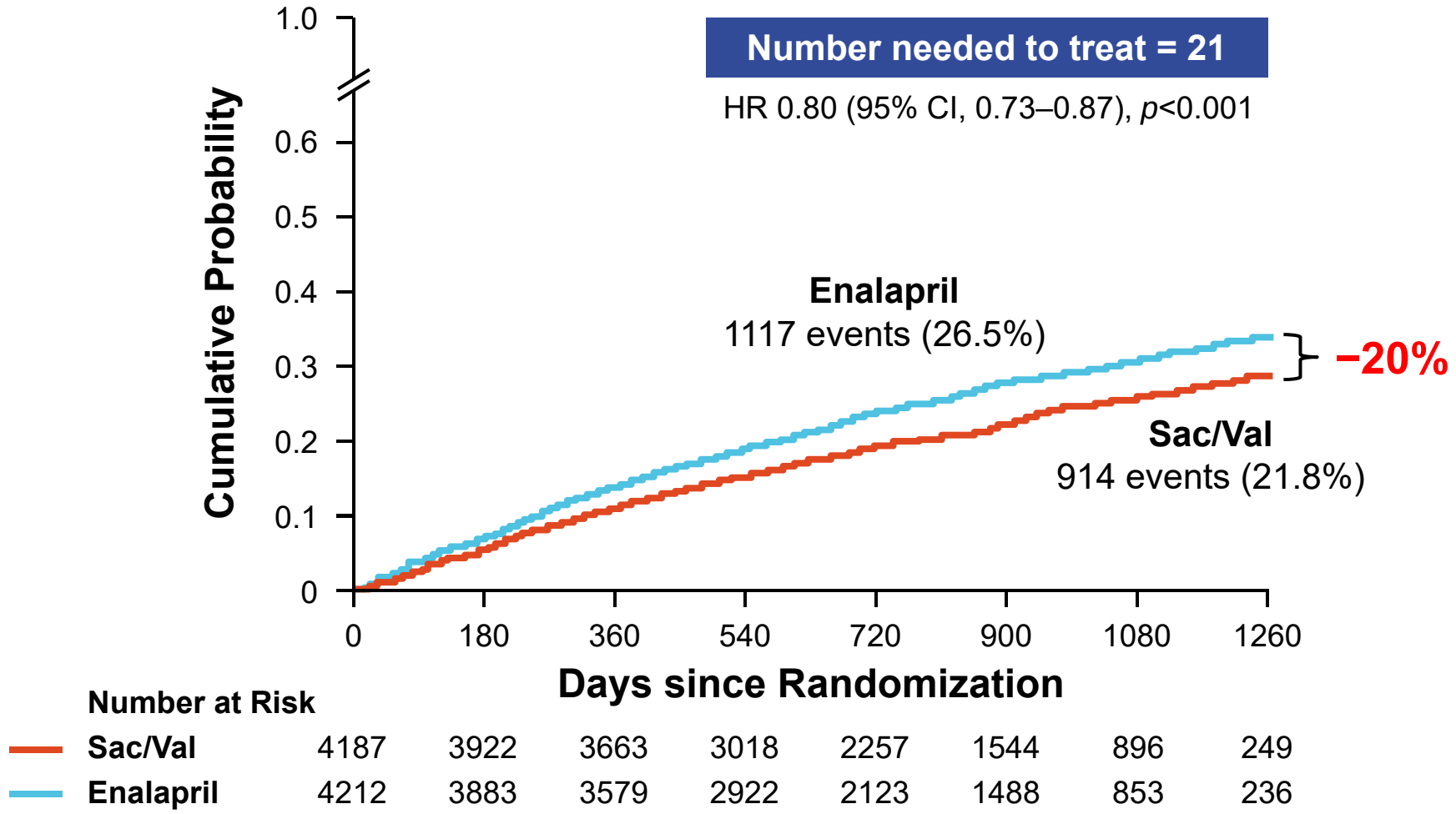
PARADIGM-HF: Baseline Characteristics

	Sac/Val (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (bpm)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/mL)	1631 (885–3154)	1594 (886–3305)
B-type natriuretic peptide (pg/mL)	255 (155–474)	251 (153–465)
History of diabetes	34.7%	34.6%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	21.9%	21.4%

ICD = implantable cardioverter defibrillation; CRT = cardiac resynchronization therapy.

McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004.

PARADIGM-HF: Primary Endpoint of CV Death or Heart Failure Hospitalization



Sac/Val = Sacubitril/Valsartan; HR = hazard ratio.

McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004.

PARADIGM-HF: Effect of Sac/Val vs. Enalapril on the Primary Endpoint and Its Components

	Sac/Val (n=4187)	Enalapril (n=4212)	Hazard Ratio (95% CI)	*p*-Value
Primary endpoint	914 (21.8%)	1117 (26.5%)	0.80 (0.73–0.87)	<0.001
All-cause mortality	711 (17.0%)	835 19.8%	0.84 (0.76–0.93)	<0.001
Cardiovascular death	558 (13.3%)	693 (16.5%)	0.80 (0.71–0.89)	<0.001
Hospitalization for heart failure	537 (12.8%)	658 (15.6%)	0.79 (0.71–0.89)	<0.001

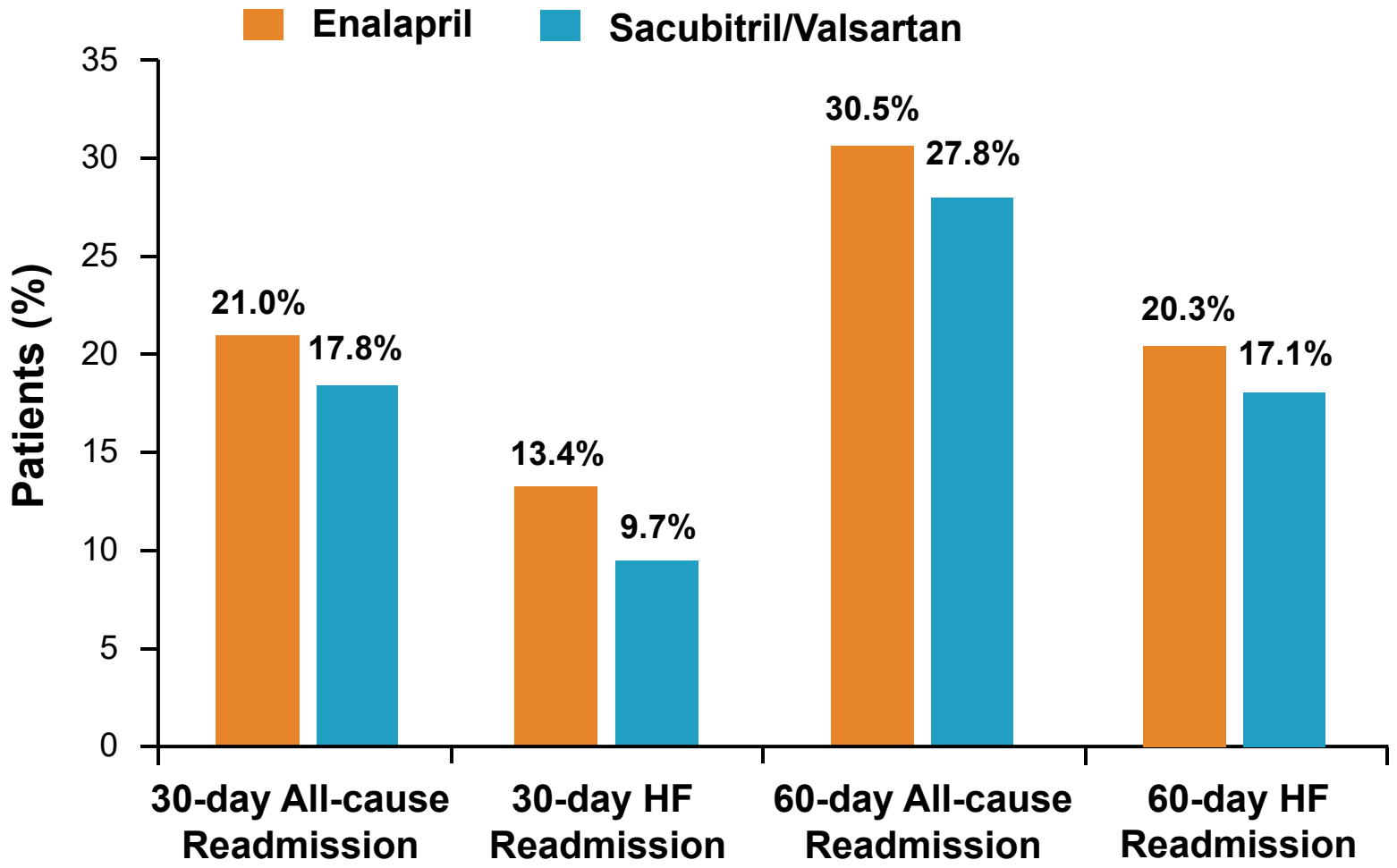
McMurray JJV, et al. *N Engl J Med.* 2014;371:993-1004.

PARADIGM-HF: Adverse Events

	Sac/Val (n=4187)	Enalapril (n=4212)	*p*-Value
Prospectively identified adverse events			
Symptomatic hypotension	14.0%	9.2%	<0.001
Serum potassium > 6.0 mmol/L	4.3%	5.6%	0.007
Serum creatinine ≥ 2.5 mg/dL	3.3%	4.5%	0.007
Cough	11.3%	14.3%	<0.001
Discontinuation for adverse event	**10.7%**	**12.3%**	**0.03**
Discontinuation for hypotension	0.9%	0.7%	0.38
Discontinuation for hyperkalemia	0.3%	0.4%	0.56
Discontinuation for renal impairment	0.7%	1.4%	0.002
Angioedema (adjudicated)			
Medications; no hospitalization	6 (0.1%)	4 (0.1%)	0.52
Hospitalized; no airway compromise	3 (0.1%)	1 (<0.1%)	0.31
Airway compromise	0	0	—

McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004.

Influence of Sacubitril/Valsartan on Readmission Rates after HF Hospitalization



Desai AS, et al. *J Am Coll Cardiol*. 2016;68(3):241-8.

PARADIGM-HF: Summary of Findings

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

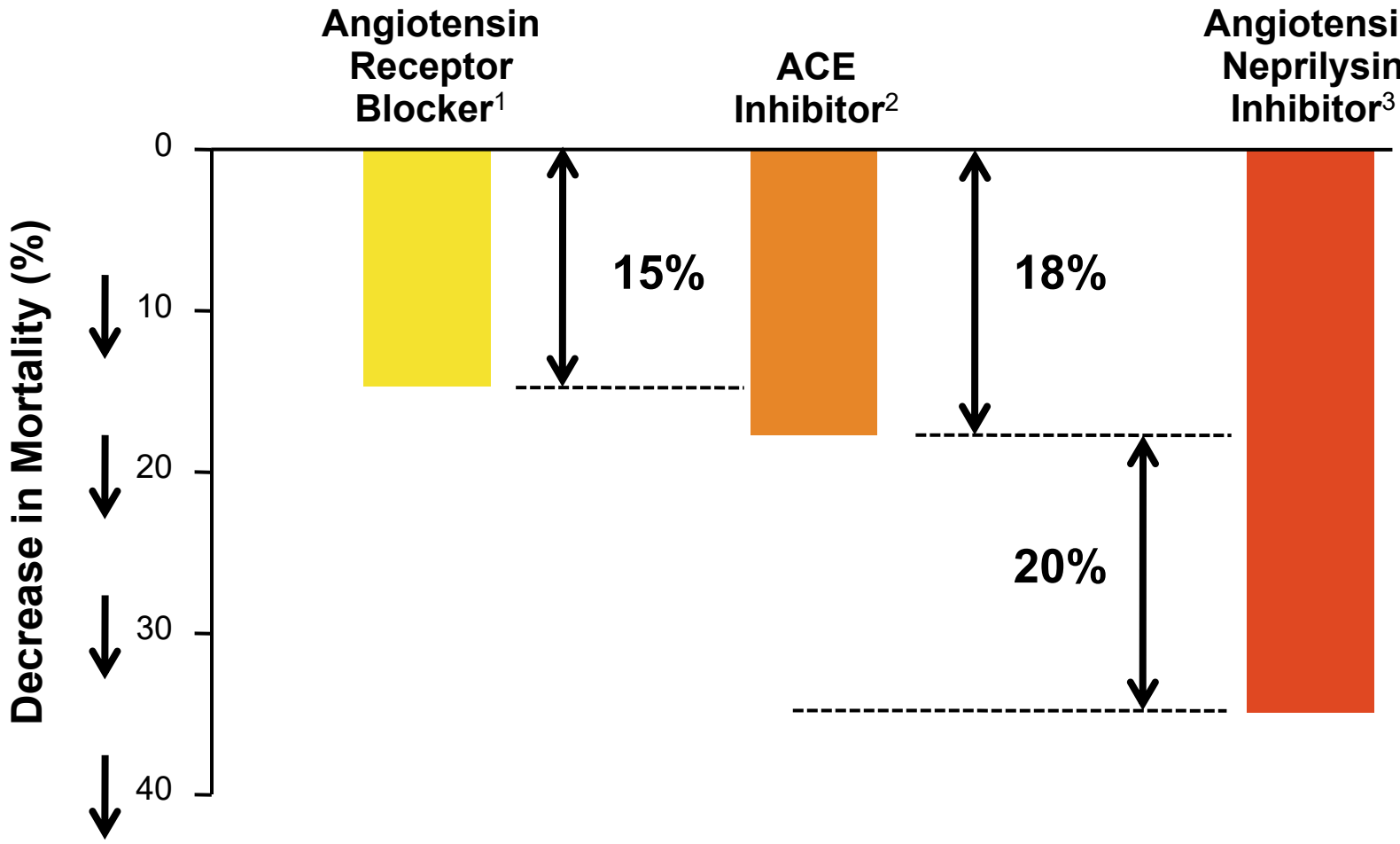
Sac/Val was *more effective* than enalapril in…

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

Sac/Val was *better tolerated* than enalapril…

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

Angiotensin Neprilysin Inhibition with Sac/Val Doubles Effect on CV Death of Current Inhibitors of the RAS



RAS = renin-angiotensin system

1. Granger CB, et al. *Lancet*. 2003;362:772-776. 2. The SOLVD Investigators. *N Engl J Med*. 1991;325:293-302.
3. McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004.

FDA-Approved Sacubitril/Valsartan

	Sacubitril/Valsartan
Indication	The fixed-dose combination of the neprilysin inhibitor sacubitril and the ARB valsartan is indicated to reduce the risk of CV death and HF hospitalization in patients with HF with reduced ejection fraction.
Dosage	Start with 49/51 mg twice daily. Double the dose after 2–4 weeks, as tolerated, to maintenance dose of 97/103 mg twice daily.
Renal/hepatic impairment	For patients not currently taking an ACEI or ARB, or for those with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or moderate hepatic impairment, start with 24/26 mg twice daily.
Switching from an ACE inhibitor	Stop ACE inhibitor for 36 hours before starting treatment.
Contraindications	History of angioedema related to previous ACE inhibitor or ARB, concomitant use of ACE inhibitors, concomitant use of aliskiren in patients with diabetes. WARNING – pregnancy, hyperkalemia.
Side effects	Hypotension, hyperkalemia, cough, dizziness, renal failure, and angioedema (0.5% sacubitril/valsartan vs. 0.2% enalapril).

http://www.pdr.net/full-prescribing-information/entresto?druglabelid=3756. Accessed October 20, 2015.

2016 ACC/AHA/HFSA Heart Failure Guideline Update

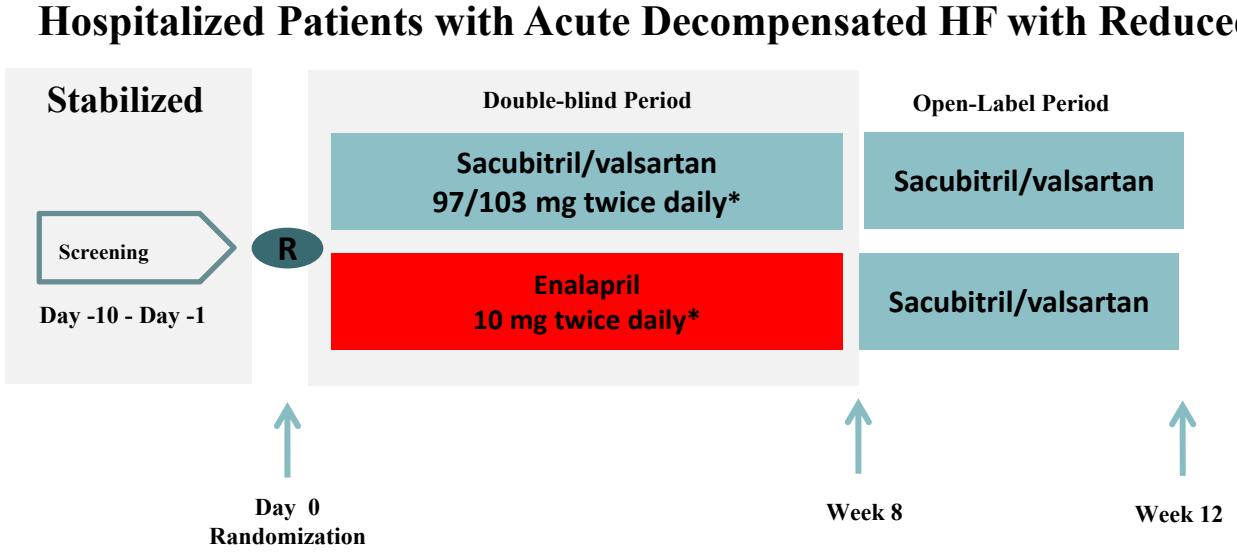
Pharmacological Treatment for Stage C HFrEF

Recommendations for RAS Inhibition with ACE Inhibitor or ARB or ARNI		
COR	**LOR**	**Recommendations**
I	**ACE: A** **ARB: A** **ARNI: B-R**	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)*, OR ARBs *(Level of Evidence: A)*, OR ARNI *(Level of Evidence: B-R)* (19) in conjunction with evidence-based beta-blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
I	**ARNI: B-R**	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.
III: Harm	**B-R**	ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.
III: Harm	**C-EO**	ARNI should not be administered to patients with a history of angioedema.

COR = class of recommendation; LOR = level of recommendation; ARNI = angiotensin receptor blocker and neprilysin inhibitor. Yancy et al. *Circulation.* 2016;134(13):e282-93 [ePUb ahead of print]

PIONEER-HF

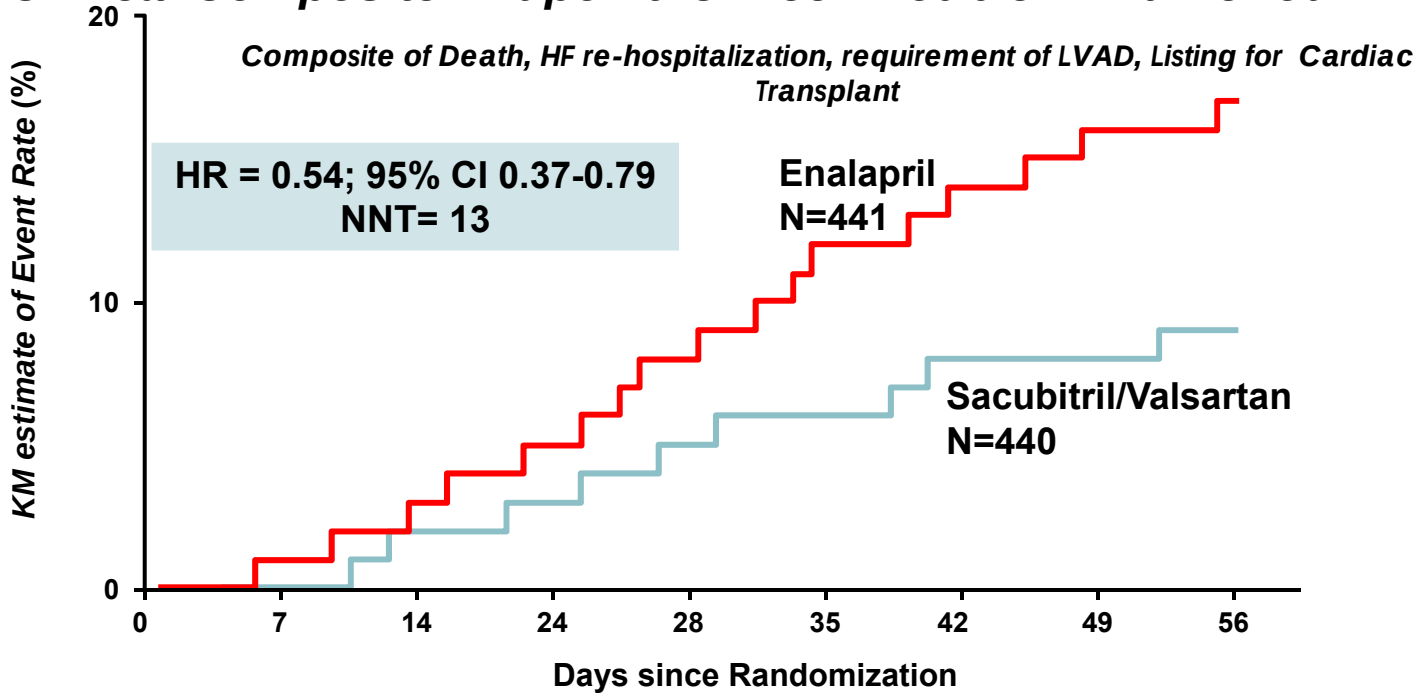
Study Design



*Target Dose
HF, Heart Failure. EF, Ejection Fraction
Velazquez et al Am Heart J 198 (2018) 145-151
Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018.
Data on File: PIONEER-HF Protocol, Novartis Pharmaceuticals Corp; October 2018

PIONEER-HF

Serious Clinical Composite Endpoint: 8-Week Double-Blind Period



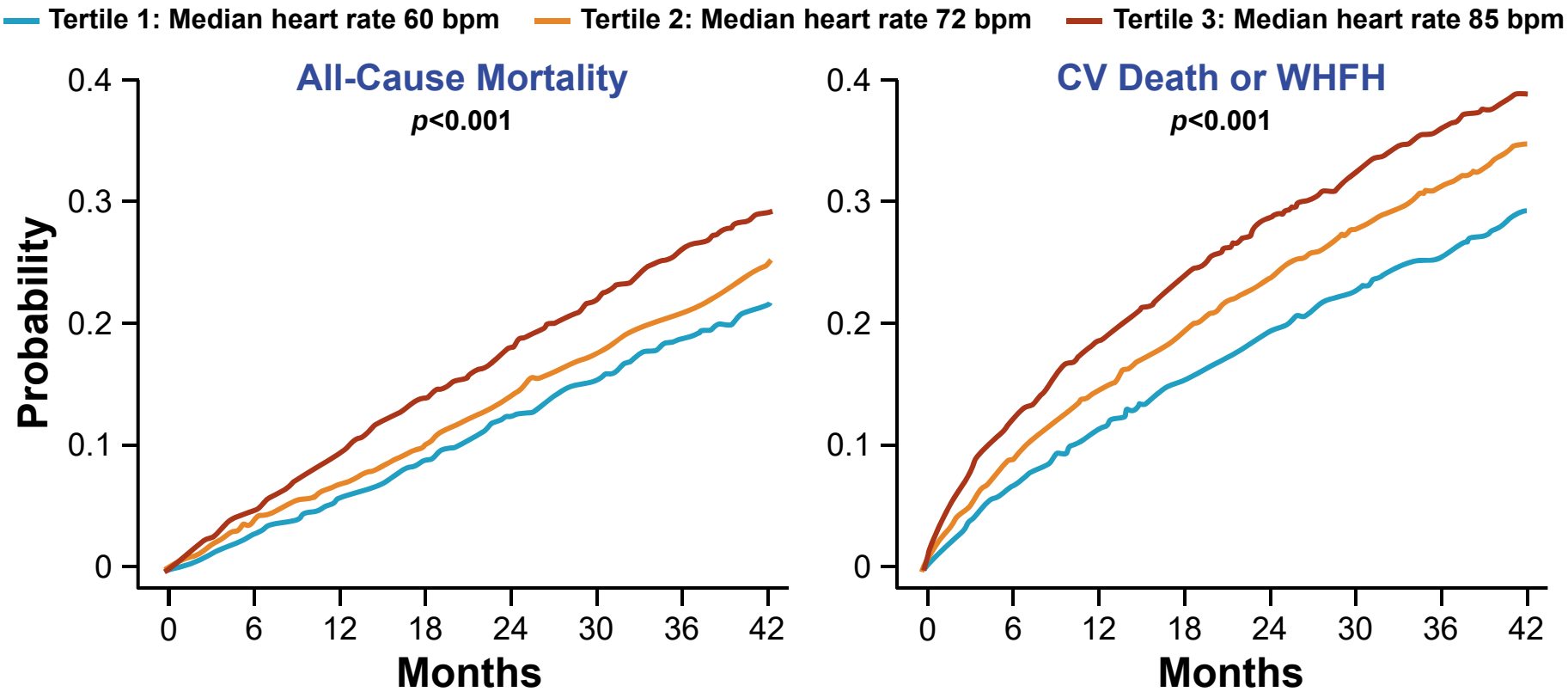
- **Serious Clinical Composite endpoint was driven by a reduction in death and HF re-hospitalizations**

CI, confidence interval; HF, heart failure; HR, hazard ratio; LVAD: Left Ventricular Assist Device

Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018

Resting Heart Rate and CV Outcomes in Patients with HF

Retrospective analysis of 7,599 symptomatic HF* patients from the CHARM studies who were followed for a median of 38 months to determine the relationship between resting heart rate at baseline and all-cause mortality and fatal and nonfatal CV outcomes.



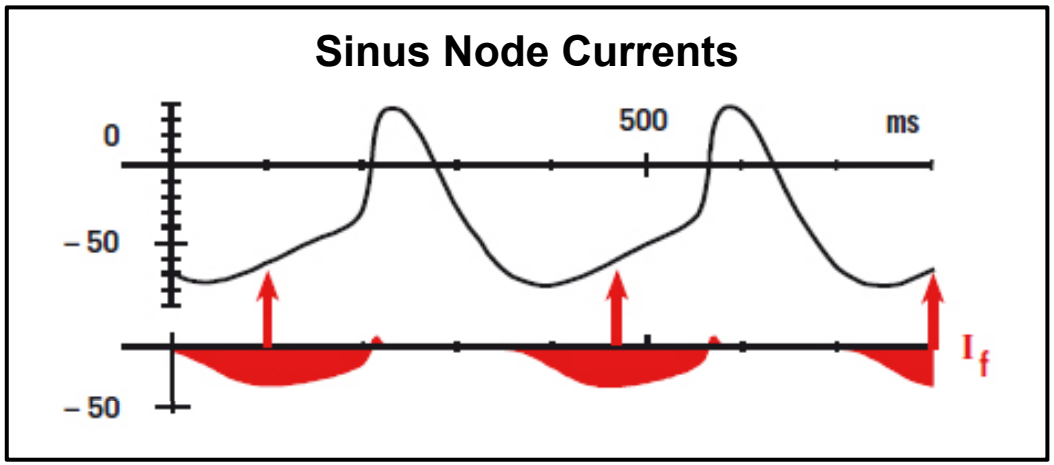
Heart rate is an important predictor of mortality and CV outcomes in patients with HF

WHFH = worsening heart failure hospitalization; *symptomatic HF defined as NYHA functional class II to IV.

Adapted from: Castagno D, et al. *J Am Coll Cardiol.* 2012;59:1785-1795.

Ivabradine

- Specific inhibitor of the **I_f current** in SA node
- This so-called **"funny" current controls** the rate of spontaneous activity of SA node myocytes
- Reduces the slope for diastolic depolarization
  - **Prolongs diastolic duration → slows heart rate**
- No action on other cardiac channels
- Does not modify cardiac contractility

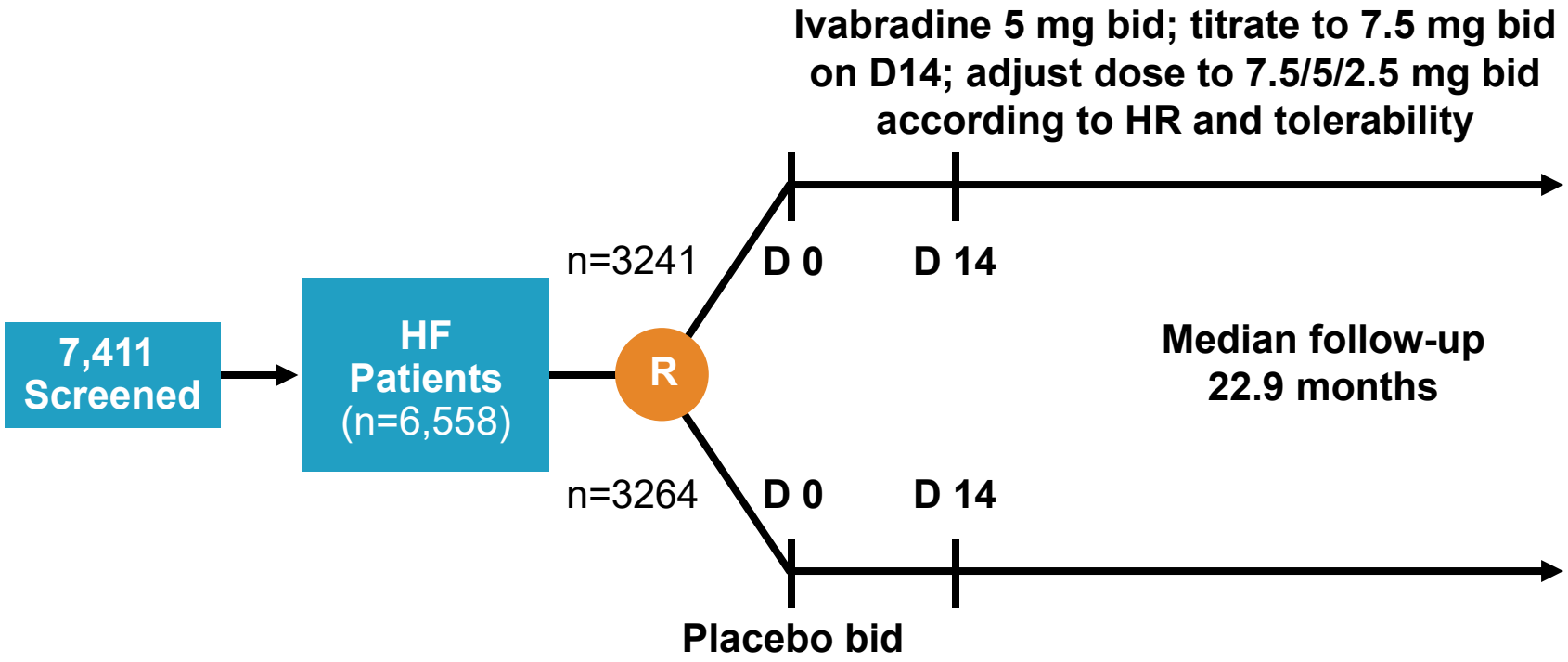


DiFrancesco D. *Pharmacol Res*. 2006;53(5):399-406. Savelieva I, Camm AJ. *Drug Saf.* 2008;31(2):95-107.

SHIFT Study: Design

Inclusion Criteria:

- ≥18 years; symptomatic HF NYHA class II to IV; ischemic/non-ischemic etiology
- LV systolic dysfunction (EF ≤35%); heart rate ≥70 bpm; sinus rhythm
- Documented hospital admission for worsening HF ≤12 months

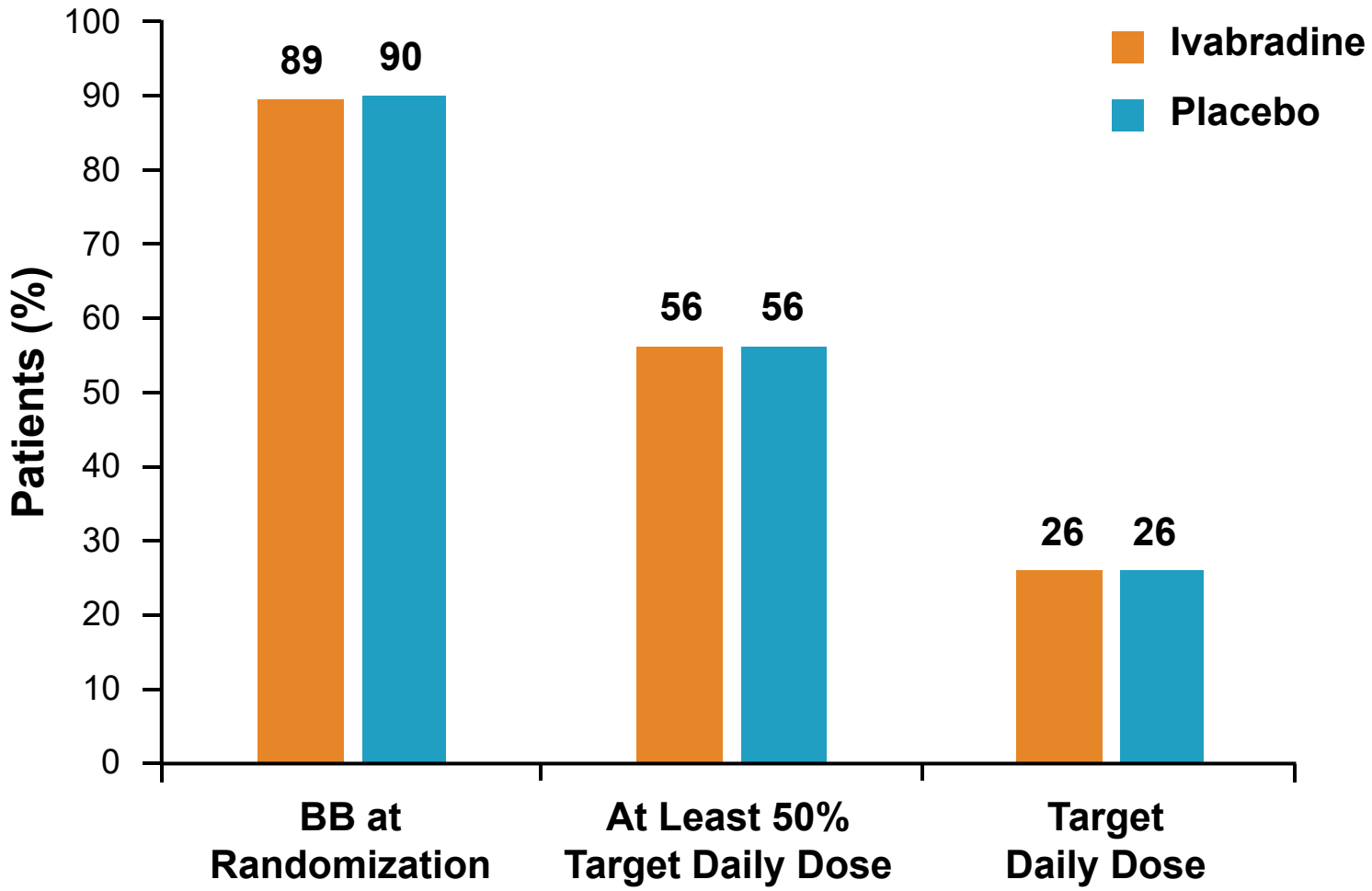


Primary endpoint: CV death or hospitalization for worsening HF

SHIFT = ivabradine and outcomes in chronic heart failure study; D 0 = day 0; D 14 = day 14.

Swedberg K, et al. *Lancet*. 2010;376:875-885.

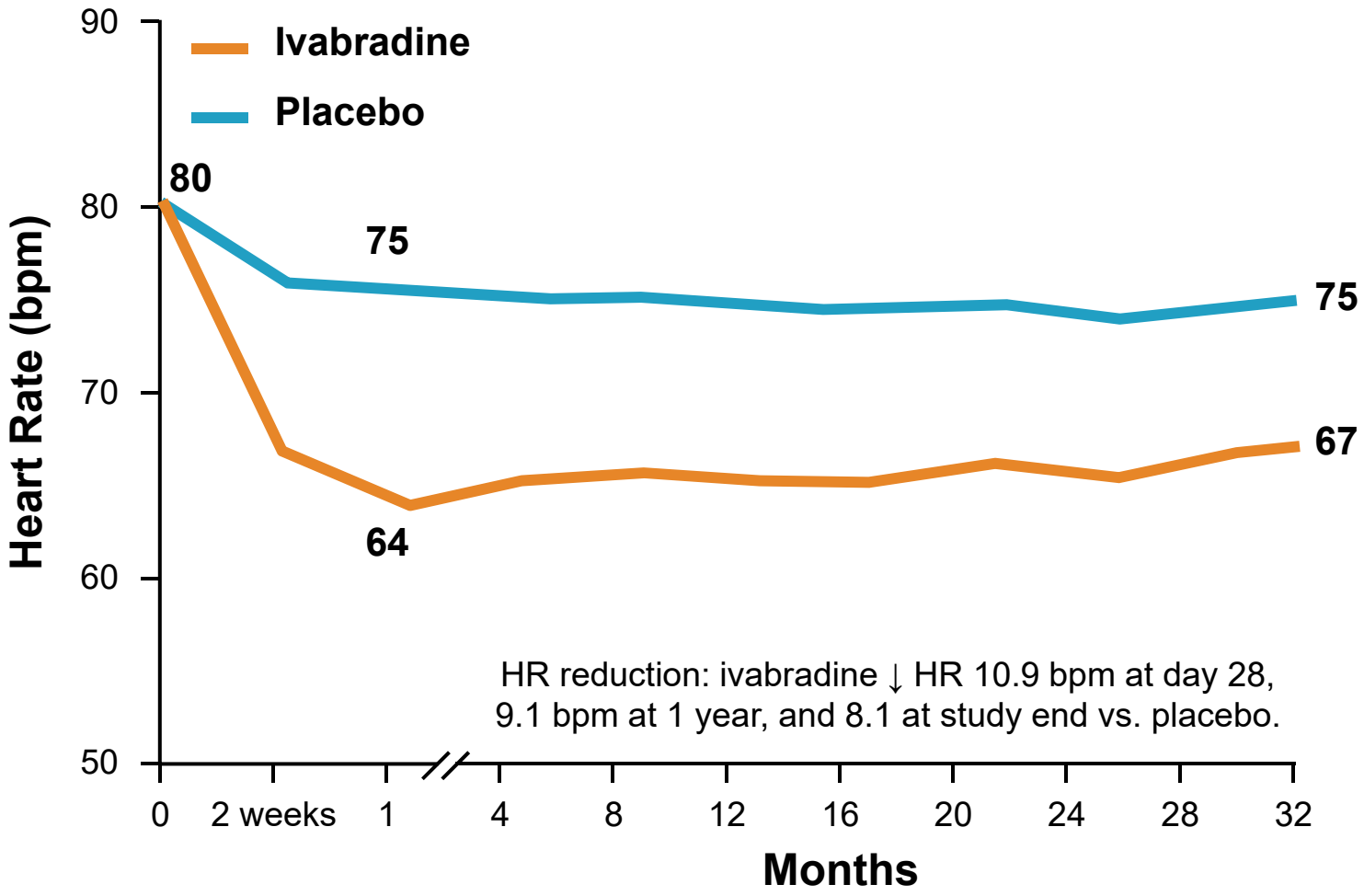
Background Beta-Blocker Treatment



Swedberg K, et al. *Lancet*. 2010;376:875-885.

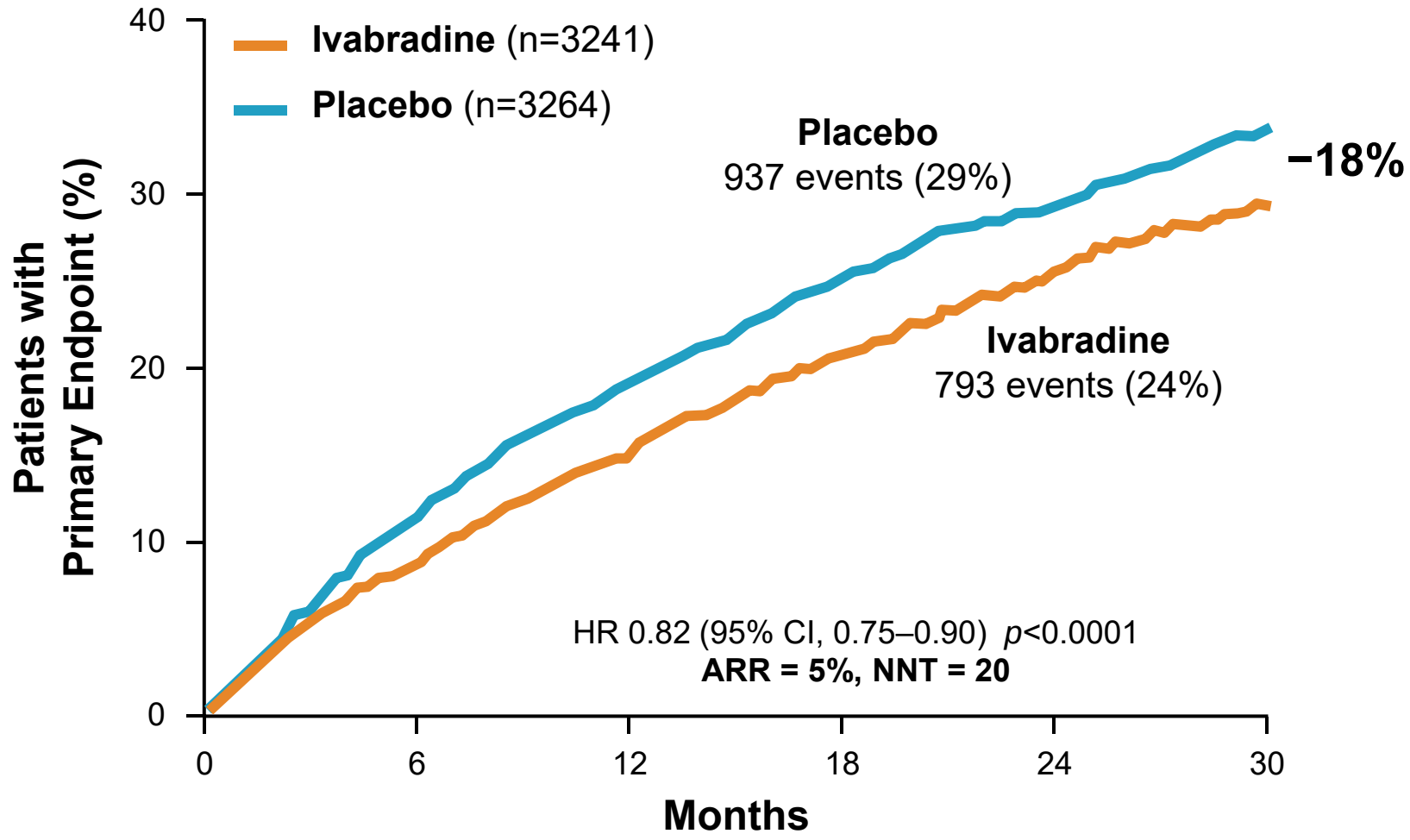
SHIFT Study: Mean Heart Rate

Mean ivabradine dose was 6.4 mg bid at 1 month and 6.5 mg bid at 1 year



Swedberg K, et al. *Lancet*. 2010;376:875-885.

SHIFT Study: Primary Endpoint of CV Death or Hospitalization for Worsening HF



ARR = absolute risk reduction; NNT = number needed to treat.

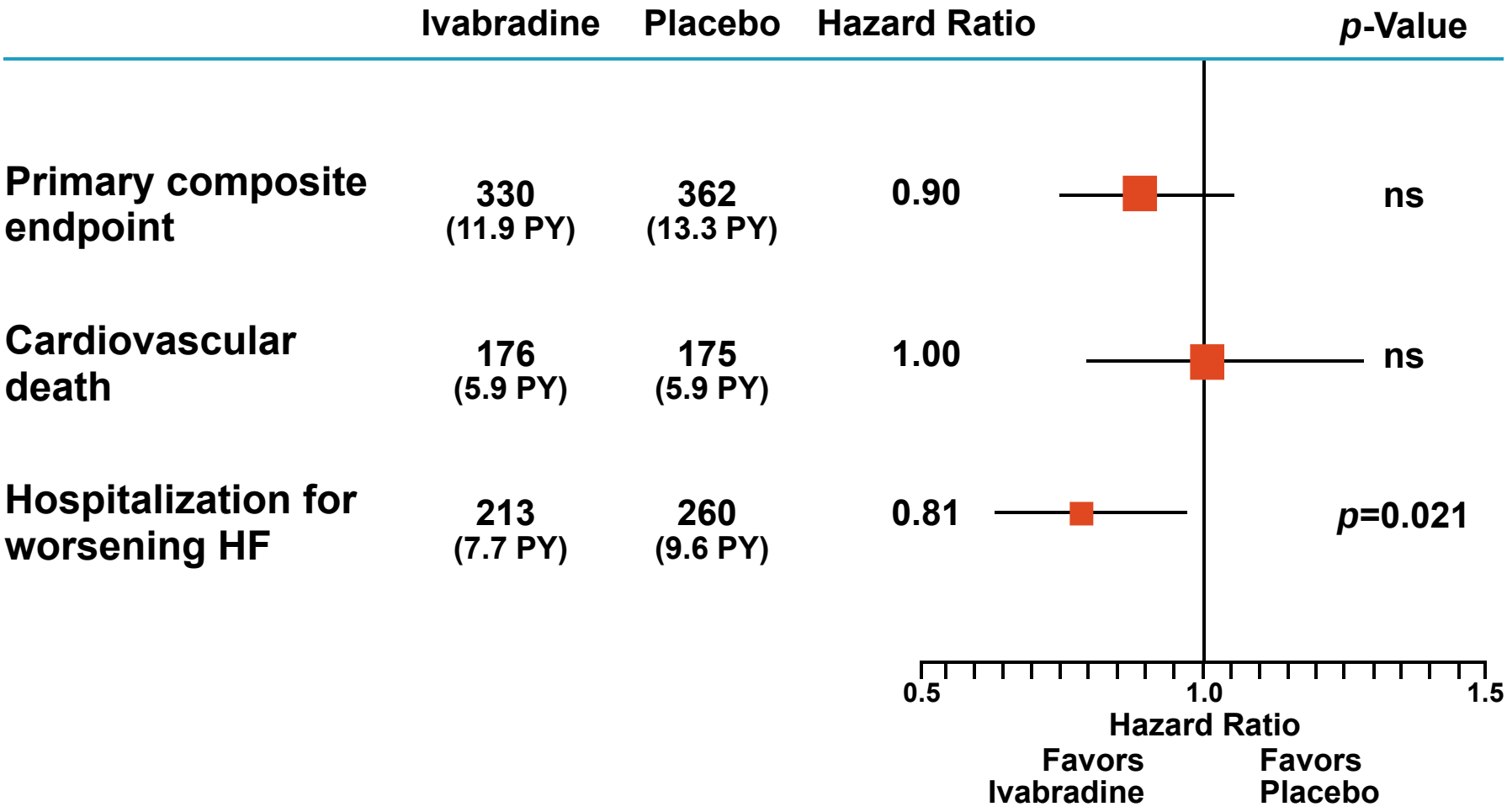
Swedberg K, et al. *Lancet*. 2010;376:875-885.

SHIFT Study: Effect of Ivabradine on Outcomes

Endpoint	Ivabradine (n=3241)	Placebo (n=3264)	HR	*p*-Value
Primary endpoint	24%	29%	0.82	<0.0001
All-cause mortality	16%	17%	0.90	0.092
Death from HF	3%	5%	0.74	0.014
All-cause hospitalization	38%	42%	0.89	0.003
Any CV hospitalization	30%	34%	0.85	0.0002
CV death, hospitalization for worsening HF, or hospitalization for non-fatal MI	25%	30%	0.82	<0.0001

Swedberg K, et al. *Lancet*. 2010;376:875-885.

SHIFT Study: Effect of Ivabradine in Patients at ≥50% BB Target Dose (n=3181)



BB = beta blocker; ns = not significant.

Swedberg K, et al. *J Am Coll Cardiol*. 2012;59(22):1938-1945.

SHIFT Study: Incidence of Selected Adverse Events

Endpoint	Ivabradine (n=3241)	Placebo (n=3264)	*p*-Value
All serious adverse events	**45%** (1450)	**48%** (1553)	**0.025**
All adverse events	**75%** (2439)	**74%** (2423)	**0.303**
Heart failure	**25%** (804)	**29%** (937)	**0.0005**
Symptomatic bradycardia	**5%** (150)	**1%** (32)	**<0.0001**
Asymptomatic bradycardia	**6%** (184)	**1%** (48)	**<0.0001**
Atrial fibrillation	**9%** (306)	**8%** (251)	**0.012**
Phosphenes	**3%** (89)	**1%** (17)	**<0.0001**
Blurred vision	**1%** (17)	**<1%** (7)	**0.042**

Phosphenes are luminous phenomena; bradycardia is defined here as resting heart rate lower than 50 bpm or the patient had signs or symptoms related to bradycardia.

Swedberg K, et al. *Lancet*. 2010;376:875-885.

Summary of SHIFT Study

- HFrEF + elevated HR is associated with poor outcomes.
  - Primary composite endpoint with placebo = 18%/yr
- Ivabradine reduced CV death or hospitalization for worsening heart failure by 18%.
  - ARR = 5%; NNT = 20
- This beneficial effect was driven mainly by a favorable effect on HF death/admission (RRR 26%).
- Treatment with ivabradine was safe and well tolerated.

RRR = relative risk reduction.

FDA-Approved Ivabradine

	Ivabradine
Indication	To reduce the risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF with LVEF ≤35% who are in sinus rhythm with resting HR ≥70 bpm and either are on maximum-tolerated doses of beta-blockers or have a contraindication to beta-blocker use.
Dosage	Start with 5 mg twice daily. After 2 weeks of treatment, adjust dose based on HR. Max is 7.5 mg twice daily. In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, start with 2.5 mg twice daily.
Contraindications	Acute decompensated HF; BP <90/50 mmHg; sick sinus syndrome or third-degree AV block unless a functioning demand pacemaker is present; resting HR <60 bpm prior to treatment; severe hepatic impairment; pacemaker dependence. WARNING – fetal toxicity.
Side effects	Occurring in ≥1% of patients are bradycardia, hypertension, atrial fibrillation, and luminous phenomena (phosphenes).

http://www.pdr.net/full-prescribing-information/corlanor?druglabelid=3713. Accessed October 20, 2015.

2016 ACC/AHA/HFSA Heart Failure Guideline Update

Pharmacological Treatment for Stage C HFrEF

Recommendation for Ivabradine		
COR	**LOR**	**Recommendations**
IIa	**B-R**	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta-blocker at maximum-tolerated dose and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37–40).

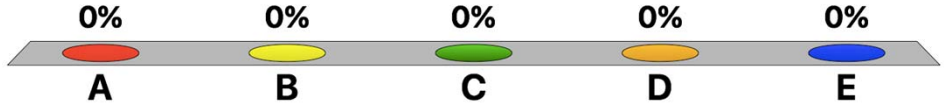
COR = class of recommendation; LOR = level of recommendation; GDEM = guideline-directed evaluation and management.

Yancy et al. *Circulation.* 2016;134:[ePub ahead of print].

Transitions of Care

After hospitalization for decompensated heart failure, the subsequent risk for mortality over the next year is:

A. <5%
B. 5-10%
C. 11-20%
✓ D. 21-30%
E. 31-40%



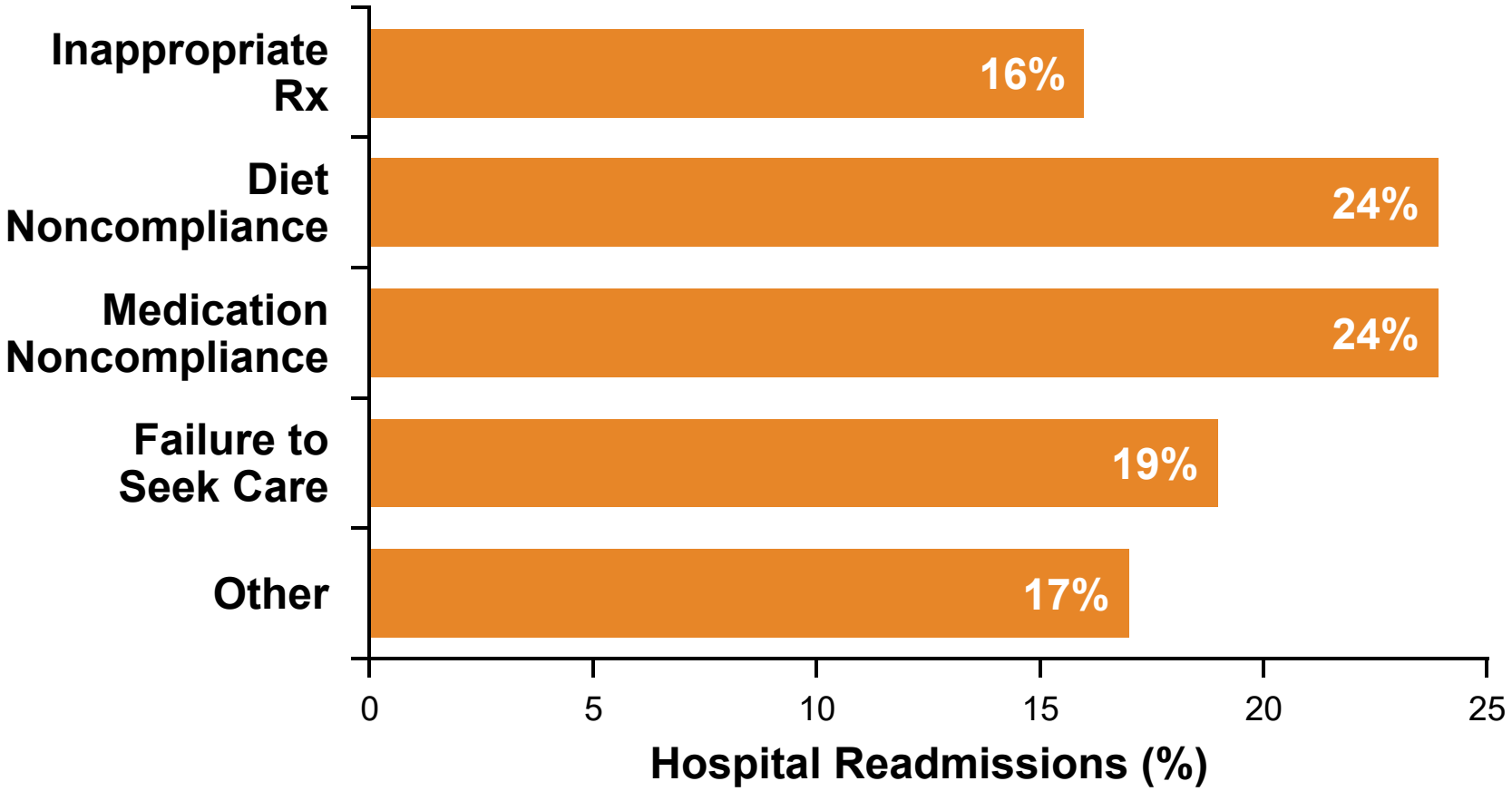
20

Rehospitalizations in Heart Failure

- Nearly one in four patients (~25%) hospitalized with HF is rehospitalized within 30 days of discharge.
- 30 day rates of rehospitalizations in HF have risen over the past 2 decades.
- Rehospitalizations for HF vary widely by hospital, even after adjusting for case mix and other factors.
- HF rehospitalizations may be preventable, but effective strategies to prevent rehospitalizations were traditionally underutilized due to lack of incentives.
- Most of the cost associated with the care of HF patients is attributable to these rehospitalizations.

Yancy CW, et al. *Circulation.* 2013;128(16):e240-327.

Causes of Hospital Readmissions for Heart Failure



Ashton CM, et al. *Ann Intern Med*. 1995;122(6):415-421.

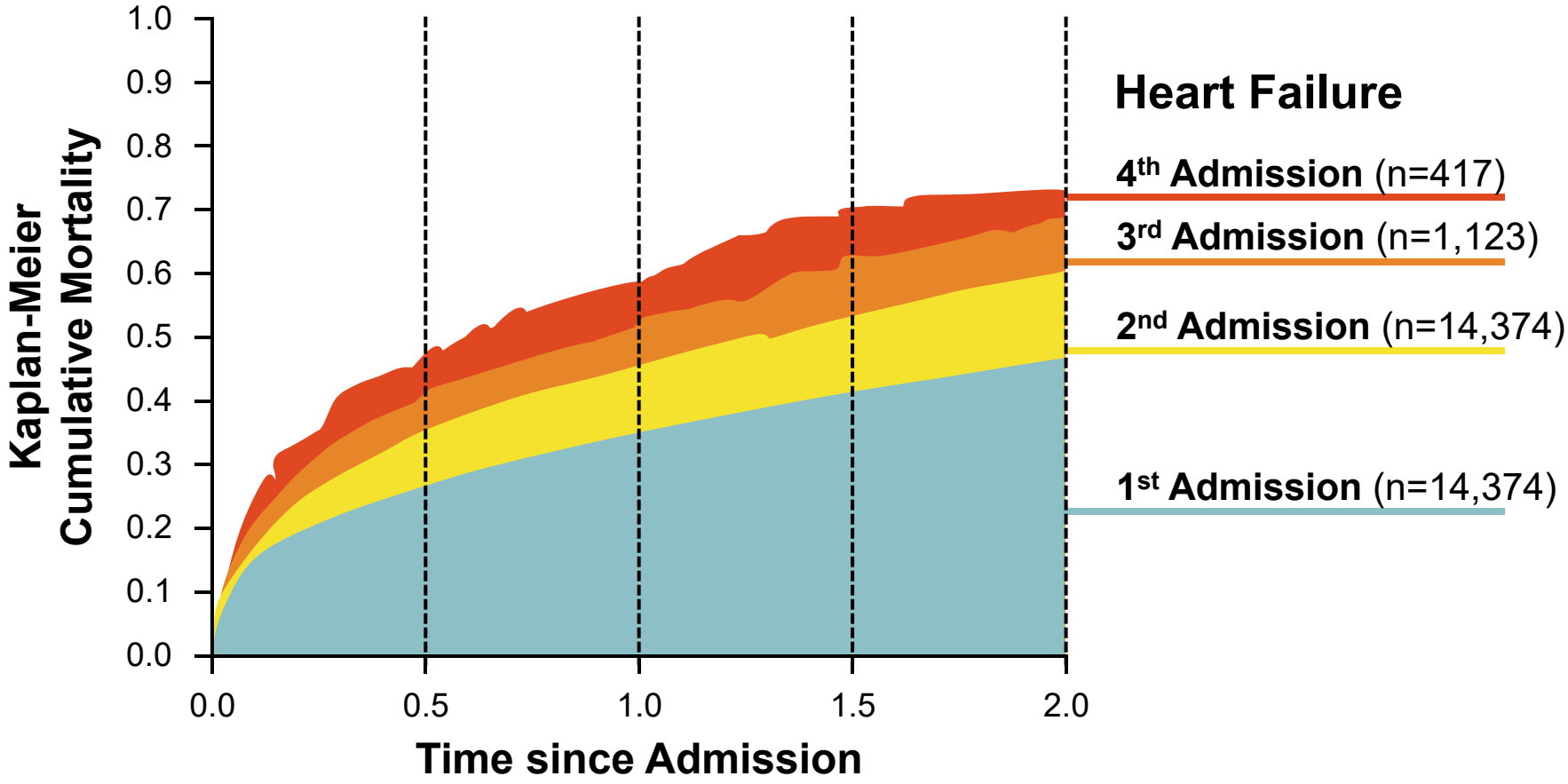
Role of Hospital-Based Providers

- Ensure patients received guideline recommended therapies
- Champion implementation of guideline-based treatment protocols
- Provide clear and comprehensive discharge instructions
- Provide HF education

Amin AN. *Am Heart Hosp J.* 2005;3(2):111-7. Yancy CW, et al. *Circulation.* 2013;128(16):e240-327.

Repeat Hospitalizations Predict Mortality

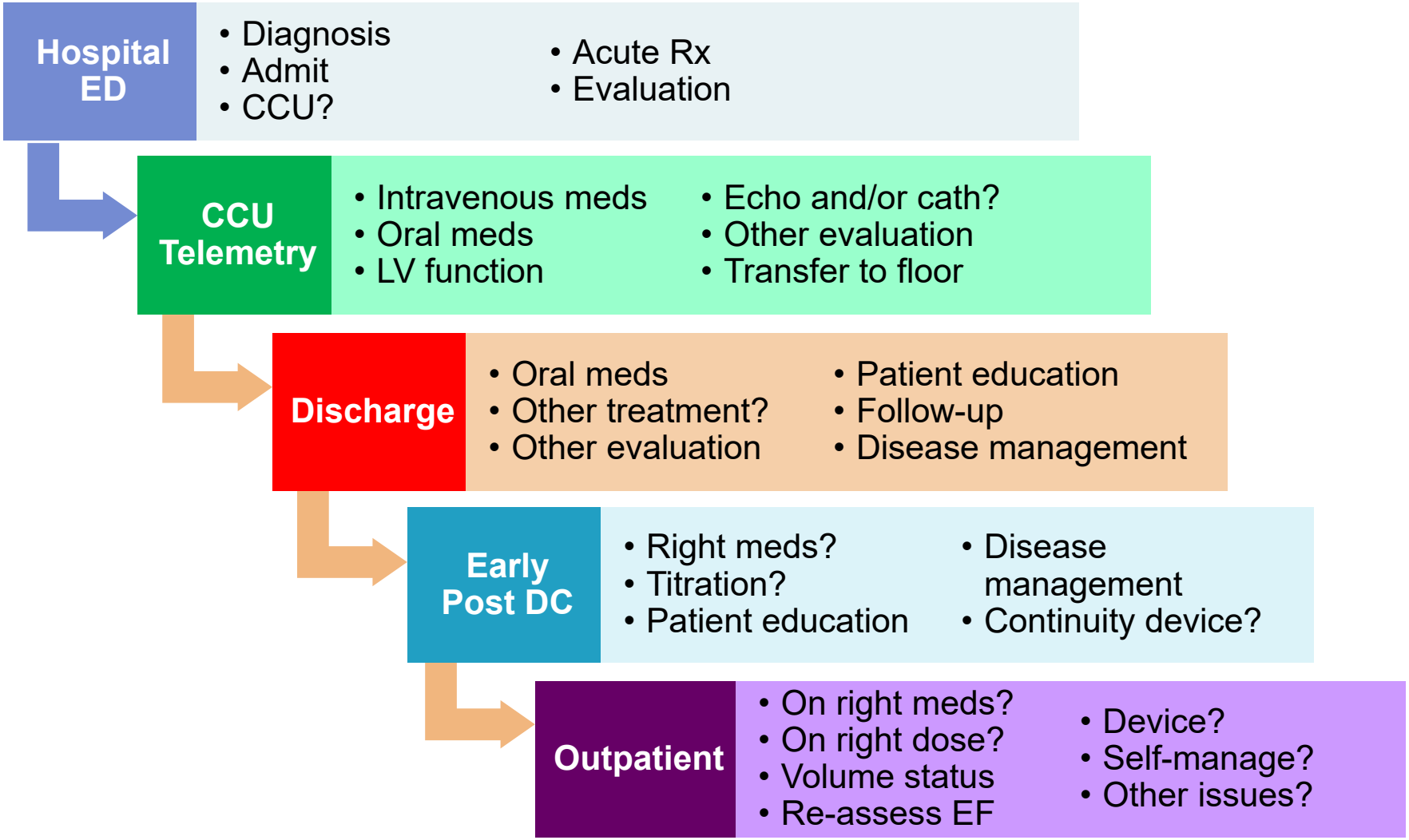
All-Cause Mortality after Each Subsequent Hospitalization for HF



Setoguchi S, et al. *Am Heart J.* 2007;154:260-266.

Continuity of HF Care

Reliable Care: Not Missing the Steps



Rx = medication(s); CCU = critical care unit.

Fonarow GC. *Rev Cardiovasc Med.* 2006;7:S3-11.

Hospital Discharge: Transitions of Care

Recommendation or Indication		
COR	**LOR**	**Recommendations**
I	**B**	Performance improvement systems in the hospital and early post discharge outpatient setting to identify HF for GDMT
I	**B**	Before hospital discharge, at the first post discharge 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 H. Palliative or hospice care

GDMT = guideline directed medical therapy.

Yancy CW, et al. *Circulation.* 2013;128(16):e240-327.

Hospital Discharge: Transitions of Care
(continued)

Recommendation or Indication		
COR	**LOR**	**Recommendations**
I	**B**	Multidisciplinary HF disease-management programs for patients at high risk for hospital readmission are recommended
I	**B**	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
IIa	**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

GDMT = guideline directed medical therapy.

Yancy CW, et al. *Circulation.* 2013;128(16):e240-327.

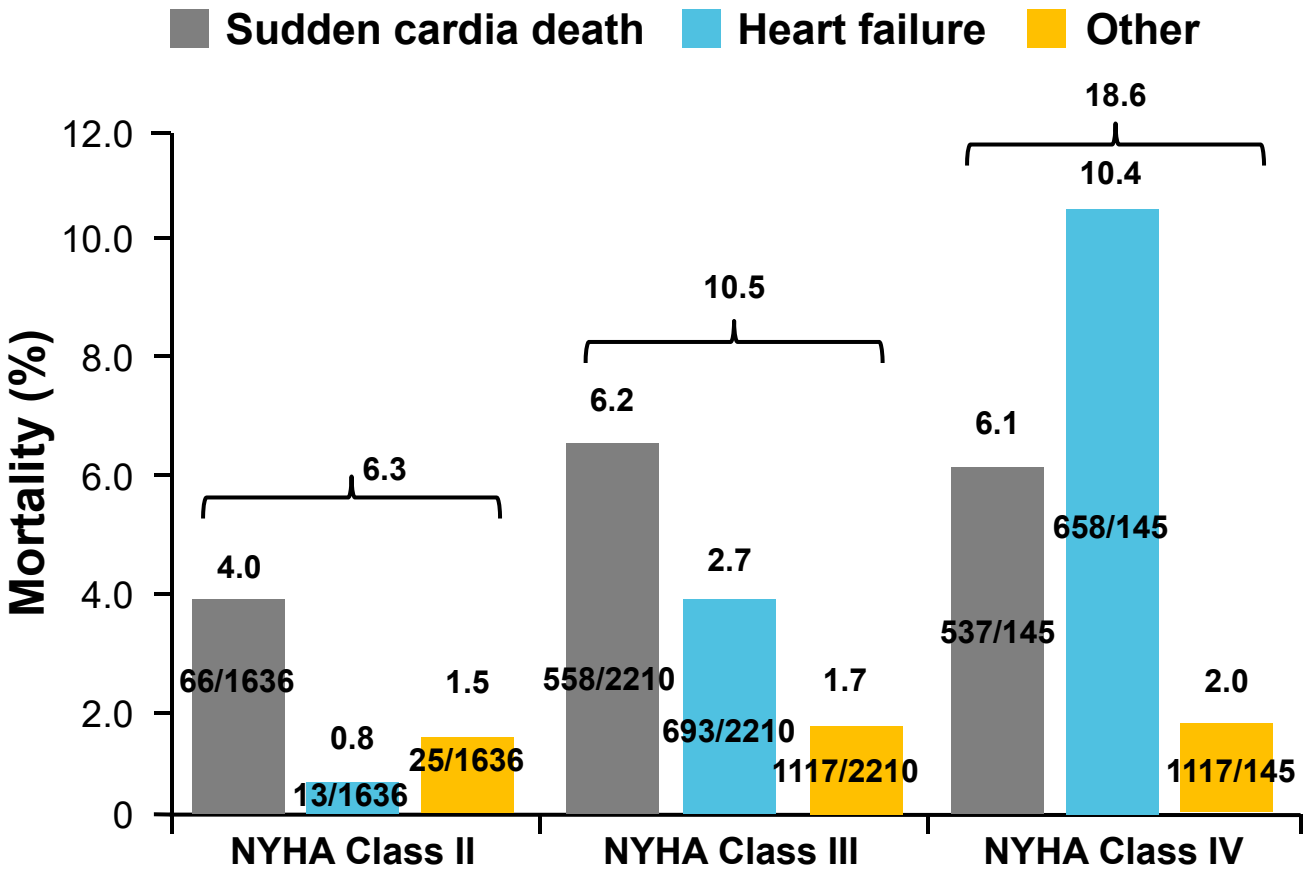
Evidence-Based Interventions to Reduce Rehospitalization in HF

- Pre-discharge HF education by trained educators
- Discharge medication programs
- Comprehensive discharge planning
- Early post-discharge physician follow-up
- Home visits by RNs and/or physicians
- Comprehensive HF disease management programs
- Implantable hemodynamic sensors

RN = registered nurse.

Yancy CW, et al. *Circulation.* 2013;128(16):e240-327.

Risk of Death High in All NYHA Functional Classifications



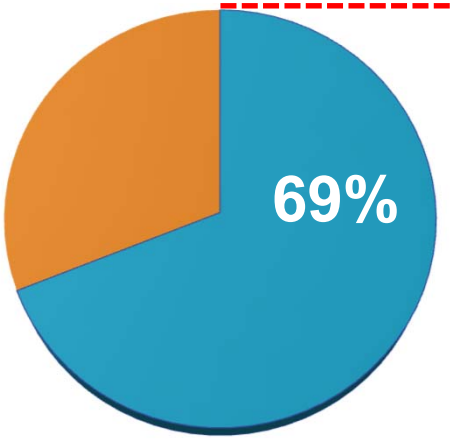
- **"Stable" patients with HFrEF on standard of care therapy still had risk of CV death or HF hospitalization**
- **25.4% of NYHA class II patients experienced CV death or HF hospitalization**
- **22.5% of patients with no prior history of HF hospitalization experienced CV death or HF hospitalization**

MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure.

1. MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007. 2. http://www.pdr.net/full-prescribing-information/Entresto-sacubitril-valsartan-3756. Accessed August 29, 2016.

"Stable" Patients with HFrEF on GDMT Remains at Risk of CV Death or HF Hospitalization

Patients with mild symptoms and physical limitations (NYHA class II) were still at risk

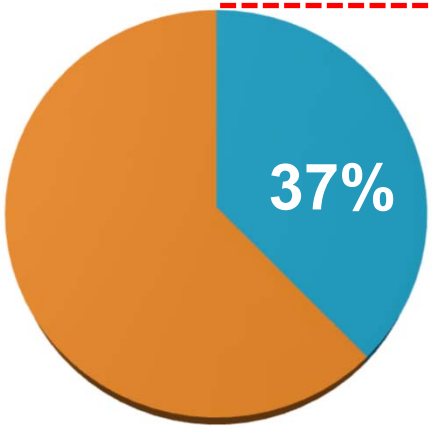


of patients randomized to enalapril were NYHA class II[1] (n=2921/4212)

25.4%

of these NYHA class II patients experienced CV death or HF hospitalization[2] (n=742/2921)

Patients with no prior history of HF hospitalization were still at risk



of patients randomized to enalapril had no prior history of HF hospitalization[1] (n=1545/4212)

22.5%

of these patients experienced CV death or HF hospitalization[2] (n=348/1545)

GDMT = guide-directed medical therapy.

1. McMurray J, et al. *N Engl J Med.* 2014;371:993-1004. 2. http://www.pdr.net/full-prescribing-information/Entresto-sacubitril-valsartan-3756. Accessed August 29, 2016.

Conclusions

- 5.7 million people in the United States have heart failure.
  - 825,000 new HF cases annually
  - Projected to increase by 46% from 2012 to 2030, resulting in >8 million people with HF
- About half of people who develop heart failure die within 5 years of diagnosis.
- There are multiple medications available for the treatment of HFrEF, including new medications that are guideline-recommended.
- There are few effective therapies for patients with normal ejection fraction HF.
- Re-admissions for HF remain a continuing and costly problem.
- Strategies to reduce readmission include early follow-up, guideline-directed therapy, and improved communication among clinicians.