How Do You Mend a Broken Heart: The New Agents to Treat HF… Paradigm Shift or Just the Same Old Drugs?

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Disclosure

- Dr. Fonarow has consulted for Amgen, Janssen, Medtronic, and Novartis, and has received research grants from the National Institutes of Health (NIH) and Medtronic.

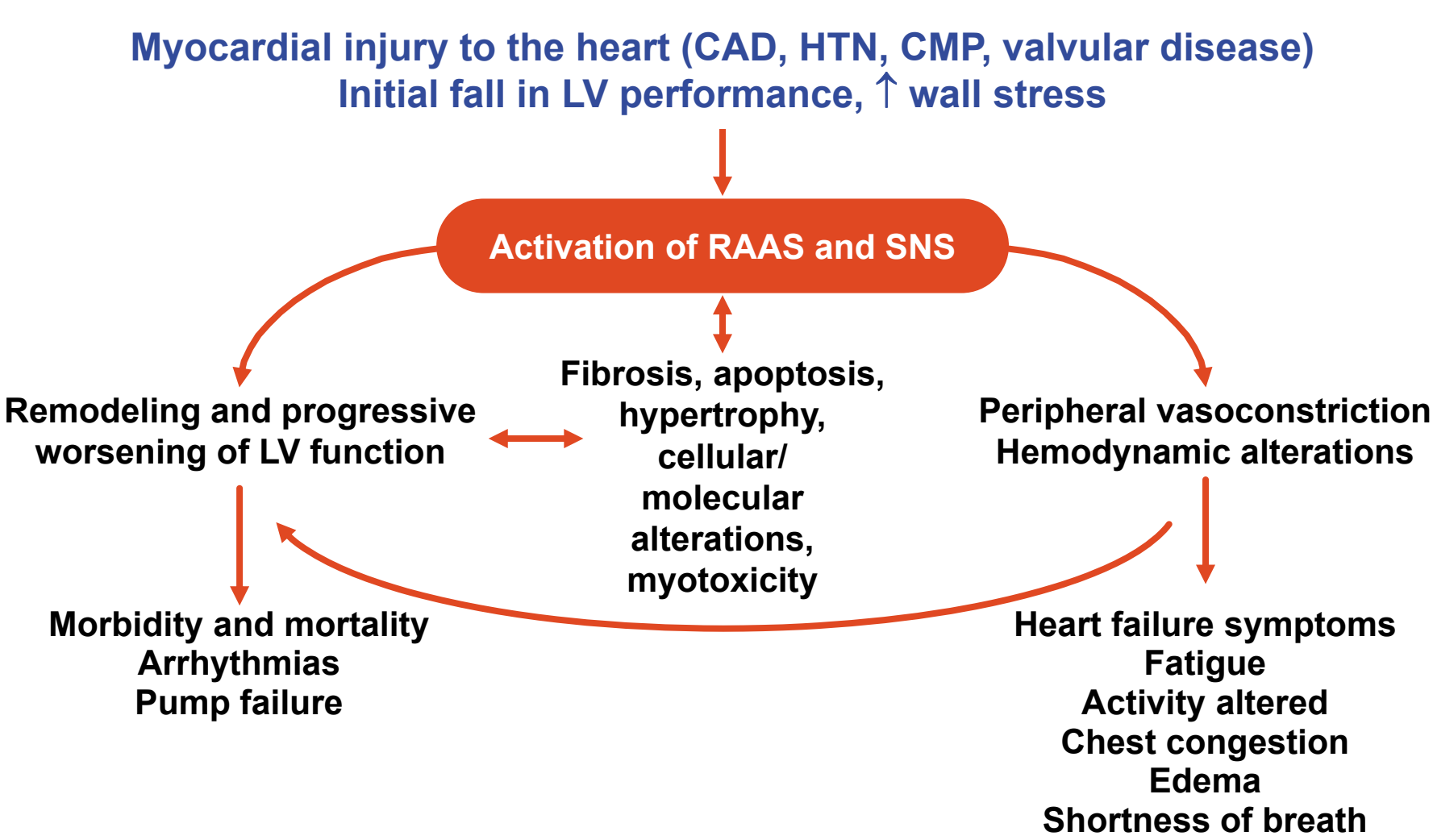
Scope of Heart Failure

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

- Heart failure (HF) is a major public health problem resulting in substantial morbidity and mortality
- 6–12 million outpatient office visits
- Despite available effective treatments, a large number of eligible patients are not receiving optimal care

Mozaffarian D, et al. *Circulation*. 2015;131:e29-e322. Jessup M. *Circulation*. 2014;129:2717-2722.

Neurohormonal Activation in Heart Failure



RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system; CMP = cardiomyopathy.

Fonarow GC. *Rev Cardiovasc Med.* 2001;2:7-12.

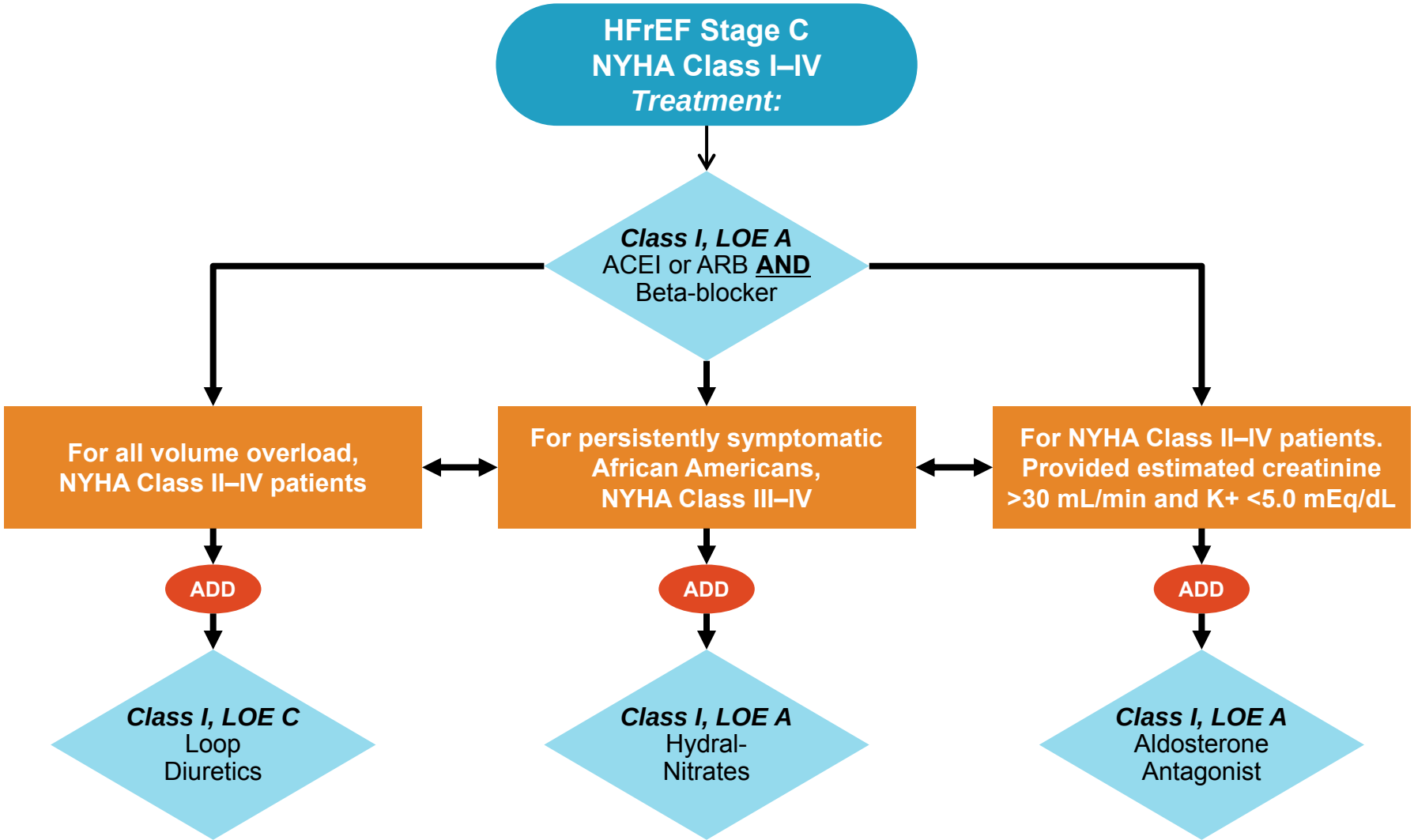
ACC/AHA HF Guidelines 2013: Management of HFrEF (Stage C)

Life-Prolonging Medical Therapy

- ACE inhibitors or ARB (Class I, evidence A) in all patients without contraindications or intolerance.
- Evidence-based beta-blockers (Class I, evidence A) in all patients without contraindications or intolerance. This would include carvedilol (immediate or extended release), metoprolol succinate, or bisoprolol.
- Aldosterone antagonists (Class I, evidence A) in all patients with Class II–IV HF without contraindications or intolerance when close monitoring can be ensured.

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

Pharmacologic Treatment for Stage C HFrEF



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

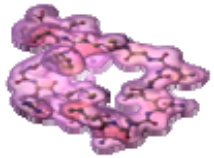
New Tools for HFrEF

Counterregulatory Peptide Systems Activated in Heart Failure Patients

Prostaglandin

Bradykinin

Adrenomedullin



NPs (Natriuretic peptides)

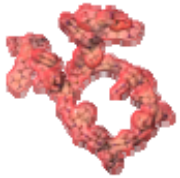
These peptides promote vasodilation, salt and water diuresis and have anti-remodeling effects that modulate the adverse effects of the RAAS and SNS

Since neprilysin breaks down these peptides, inhibitors of this enzyme should increase their levels and effects in heart failure

ANP

BNP

CNP



Urodilatin

Dendroaspis

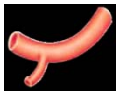
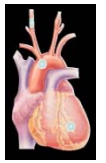
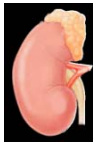
ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; NP, natriuretic peptide; NPS, natriuretic peptide system.

Mann DL et al. *Braunwald's Heart Disease*. 10th ed. Philadelphia, PA: Saunders; 2015.

Effects of Neprilysin Inhibition in Heart Failure

Endogenous vasoactive peptides

(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

- Neurohormonal activation 
- Vascular tone 
- Cardiac fibrosis, hypertrophy 
- Sodium retention 

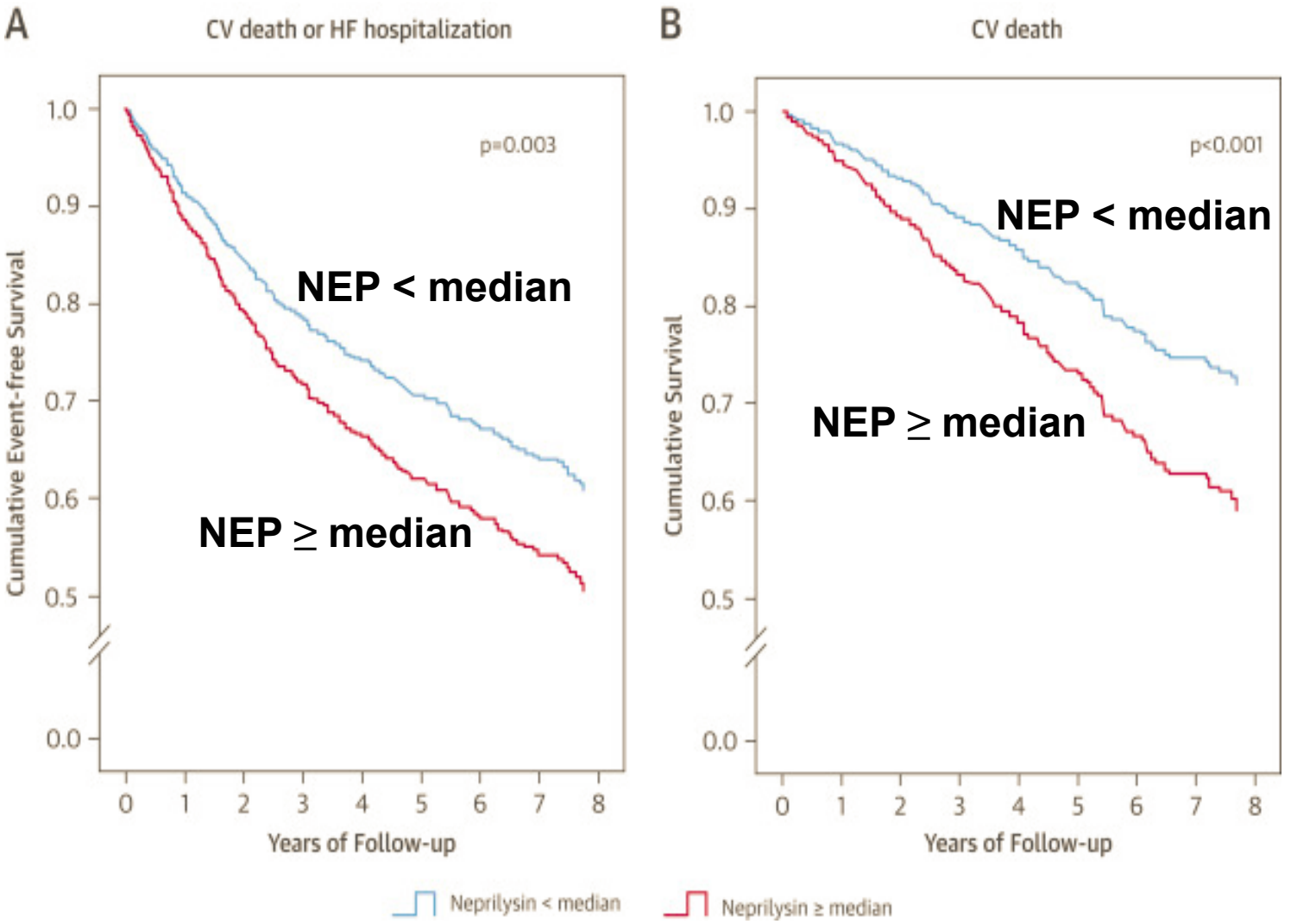
Neprilysin

Neprilysin inhibition

Inactive metabolites

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

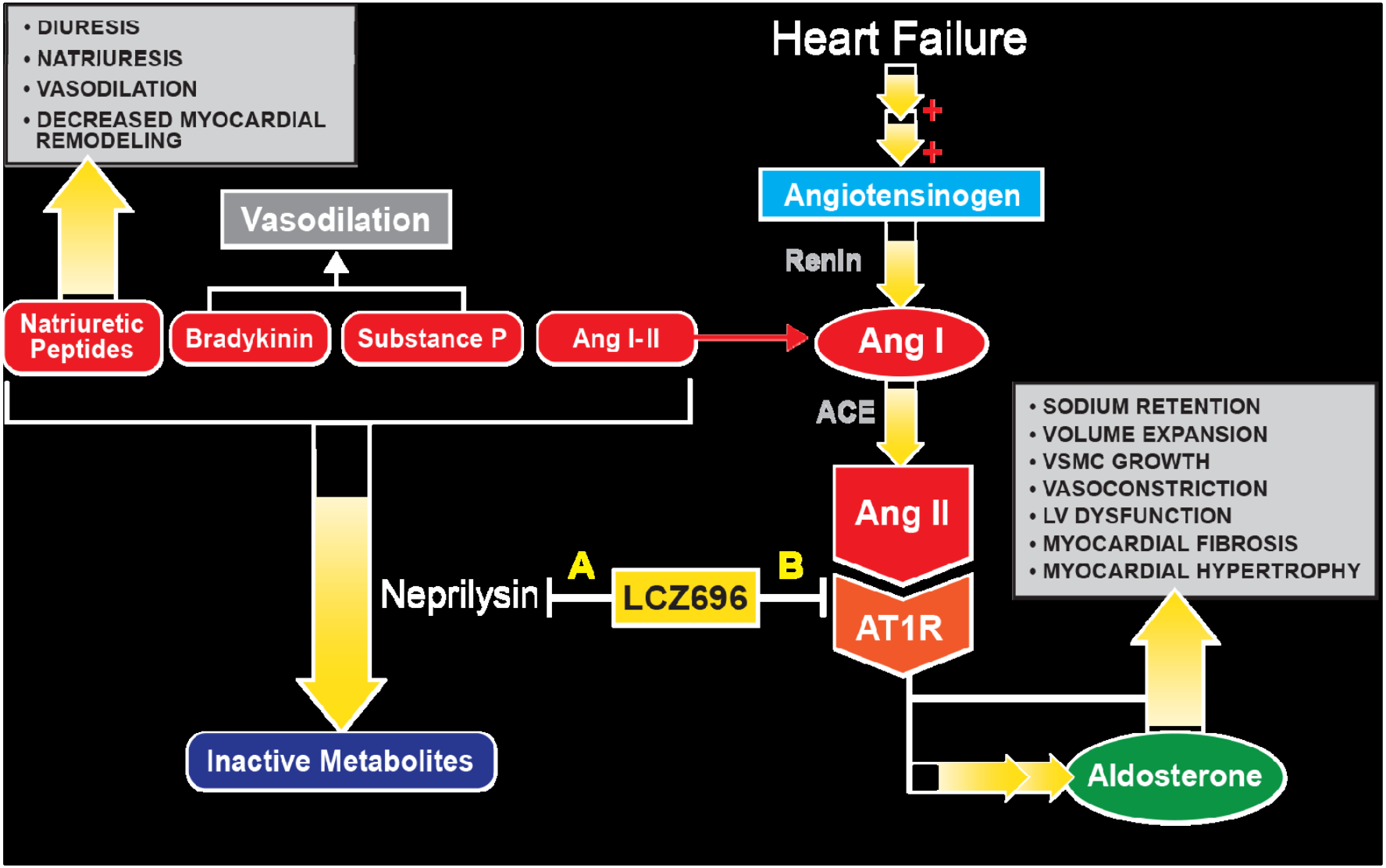
Neprilysin Levels in Blood Predict Outcomes in HF Patients



Bayés-Genís A et al. JACC 65: 657-665, 2014

Sacubitril/Valsartan (LCZ696)

Mechanism of Action



Buggey et al. Journal of Cardiac Failure, Volume 21, Issue 9, 2015, 741–750

Aim of the PARADIGM-HF Trial

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

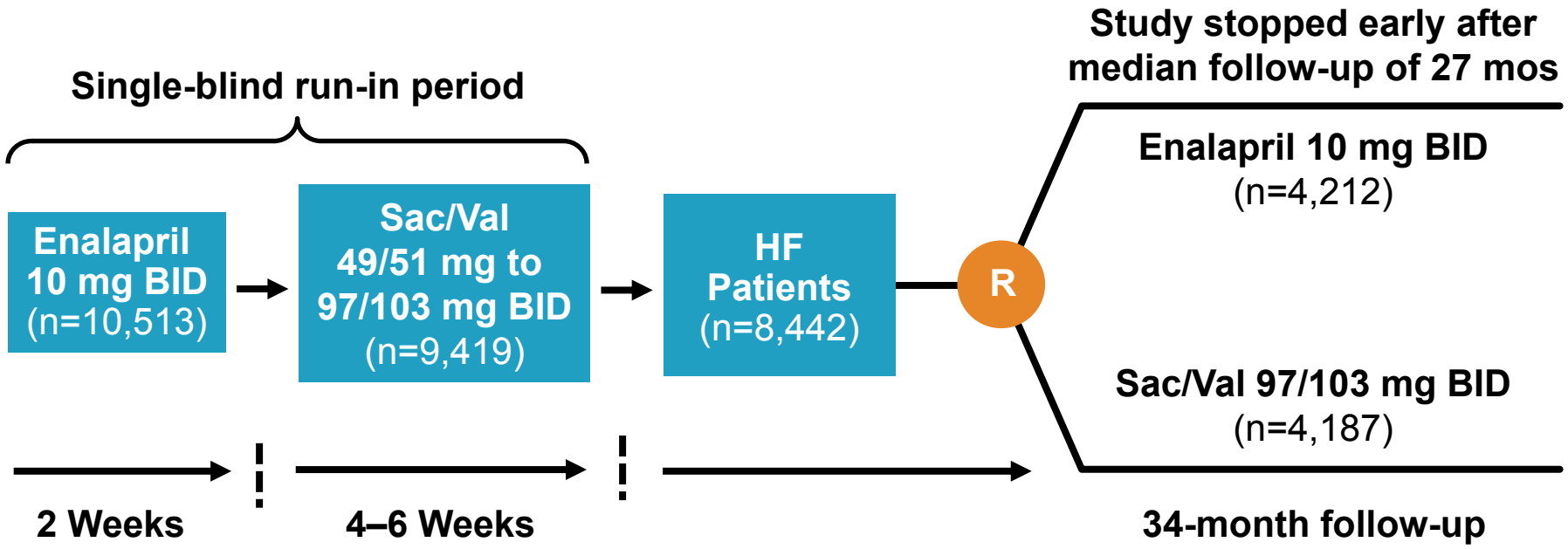
Sacubitril/Valsartan 97/103 mg twice daily ⟷ **Enalapril 10 mg twice daily**

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE

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 mos
- 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

Sac/Val = Sacubitril/Valsartan.

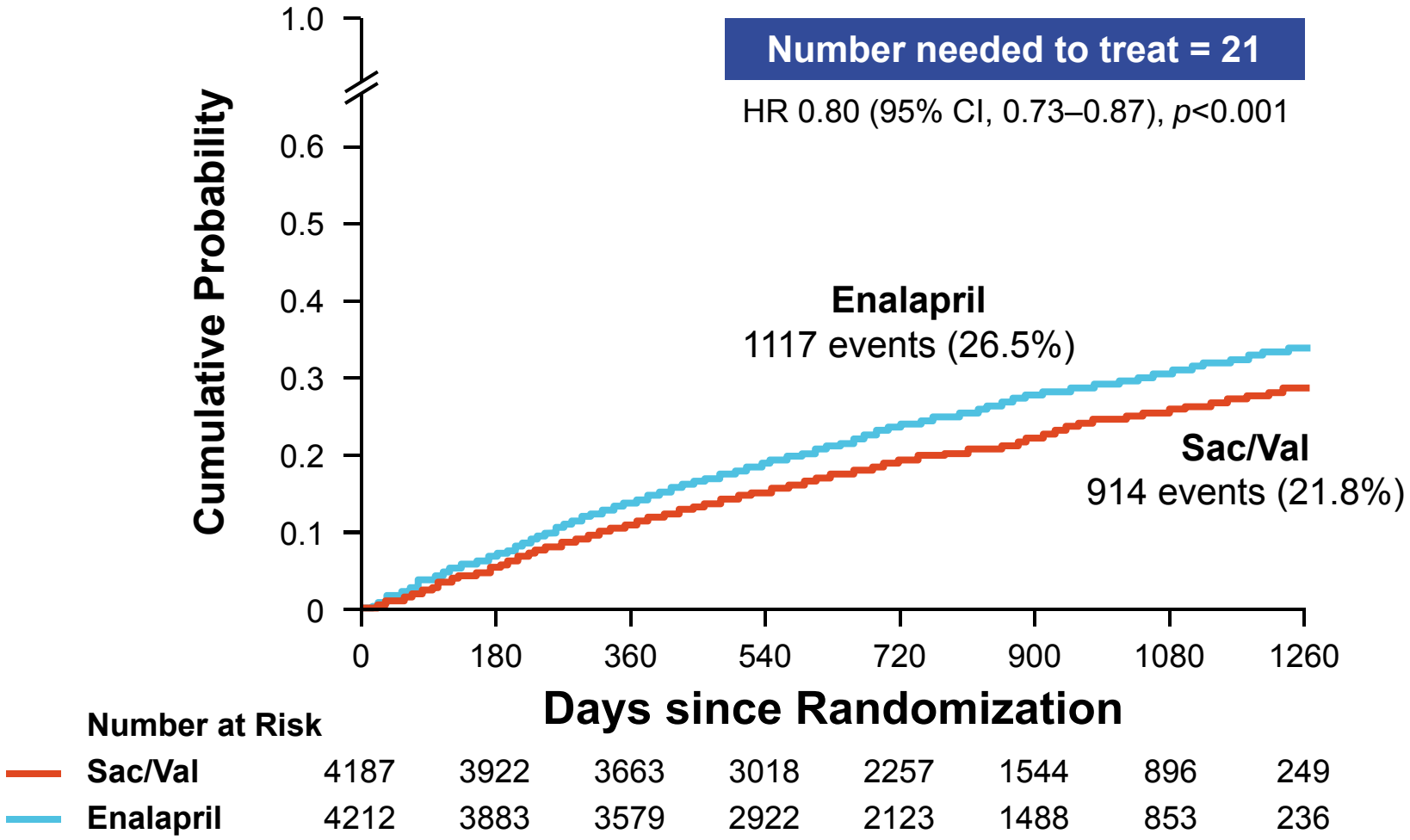
McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004.

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 (beats/min)	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%

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

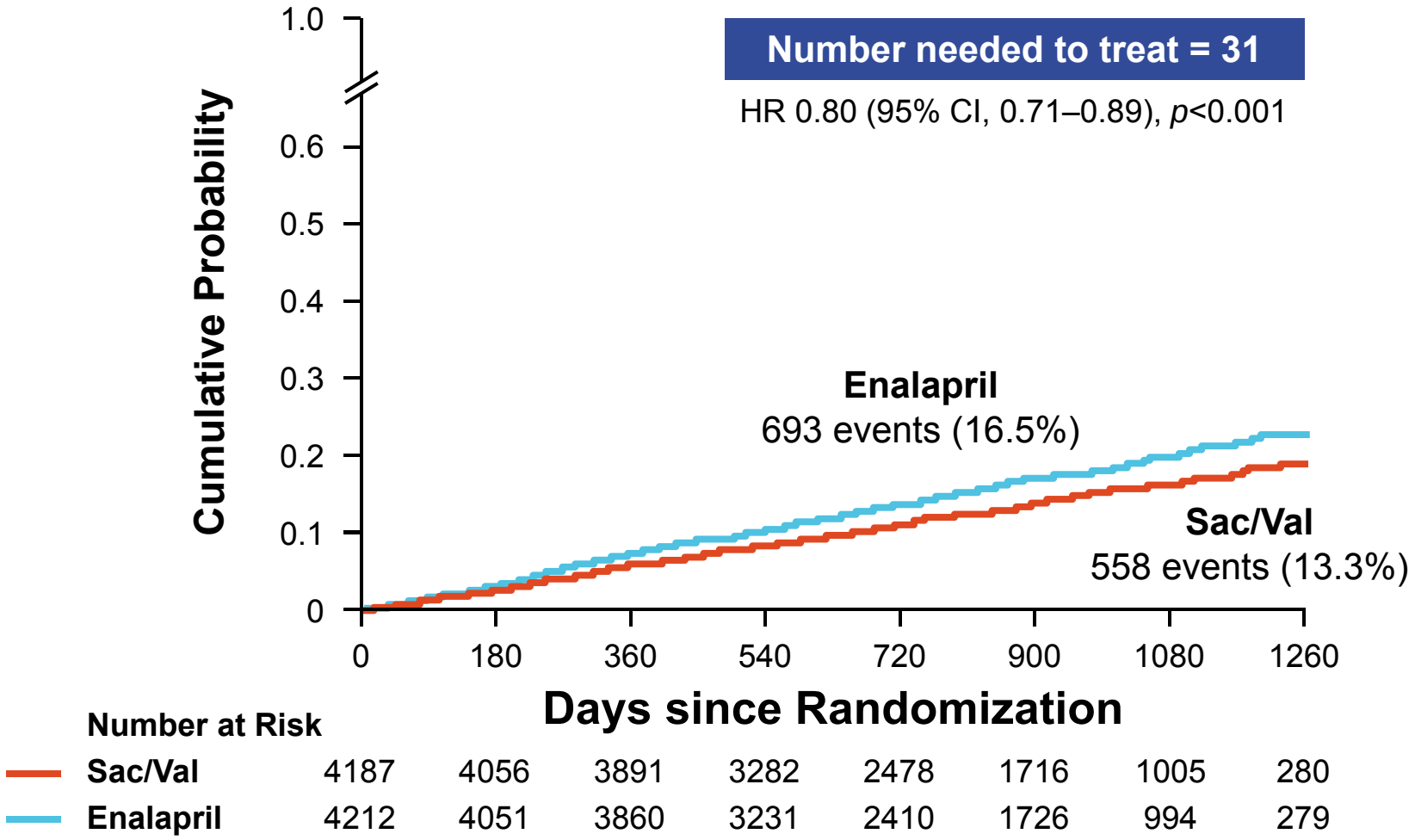
PARADIGM-HF: Primary Endpoint of CV Death or Heart Failure Hospitalization



Sac/Val = Sacubitril/Valsartan.

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

PARADIGM-HF: CV Death



Sac/Val = Sacubitril/Valsartan.

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

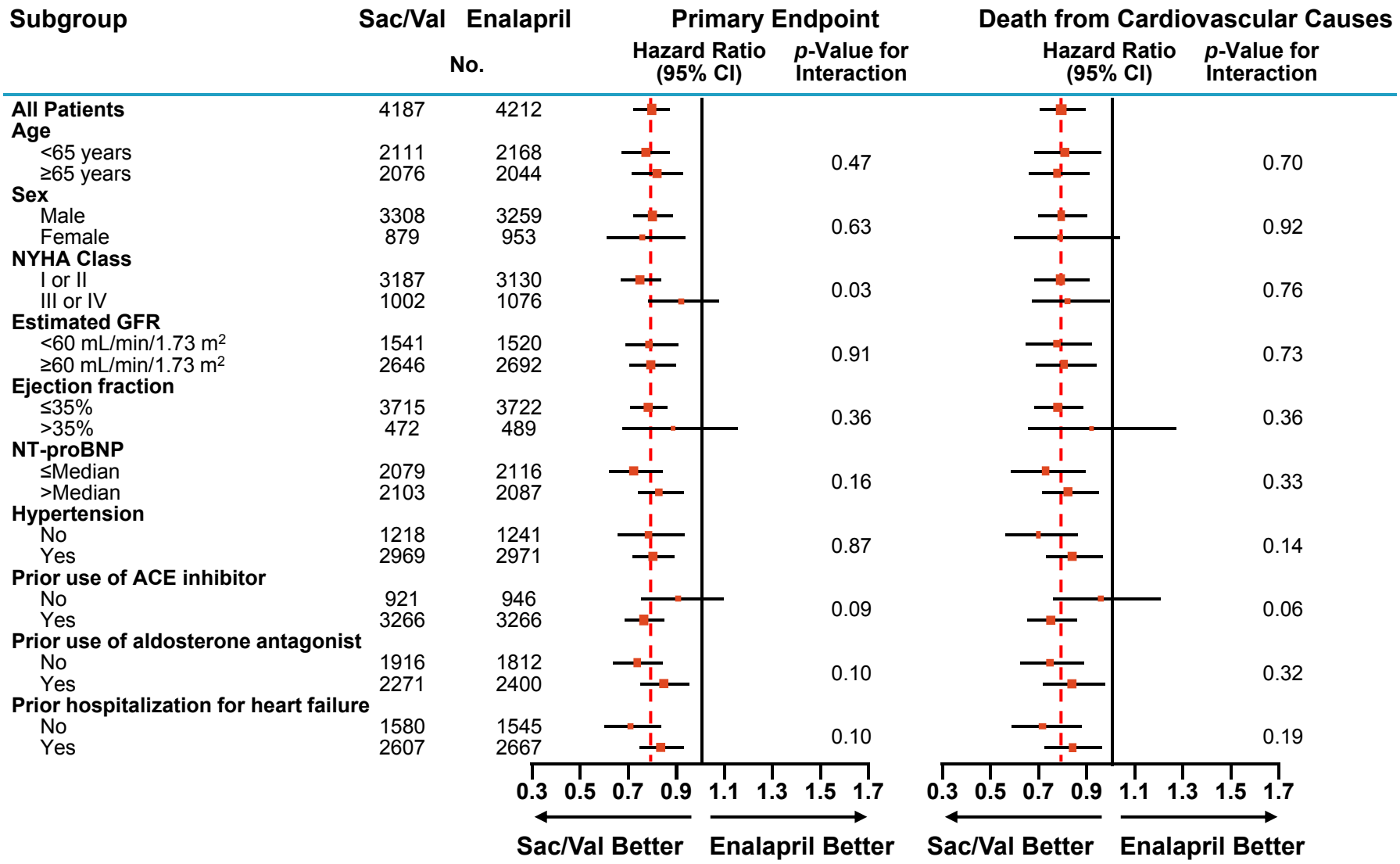
PARADIGM-HF: Effect of Sac/Val vs. Enalapril on the Primary Endpoint and Its Components

	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
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

Sac/Val = Sacubitril/Valsartan.

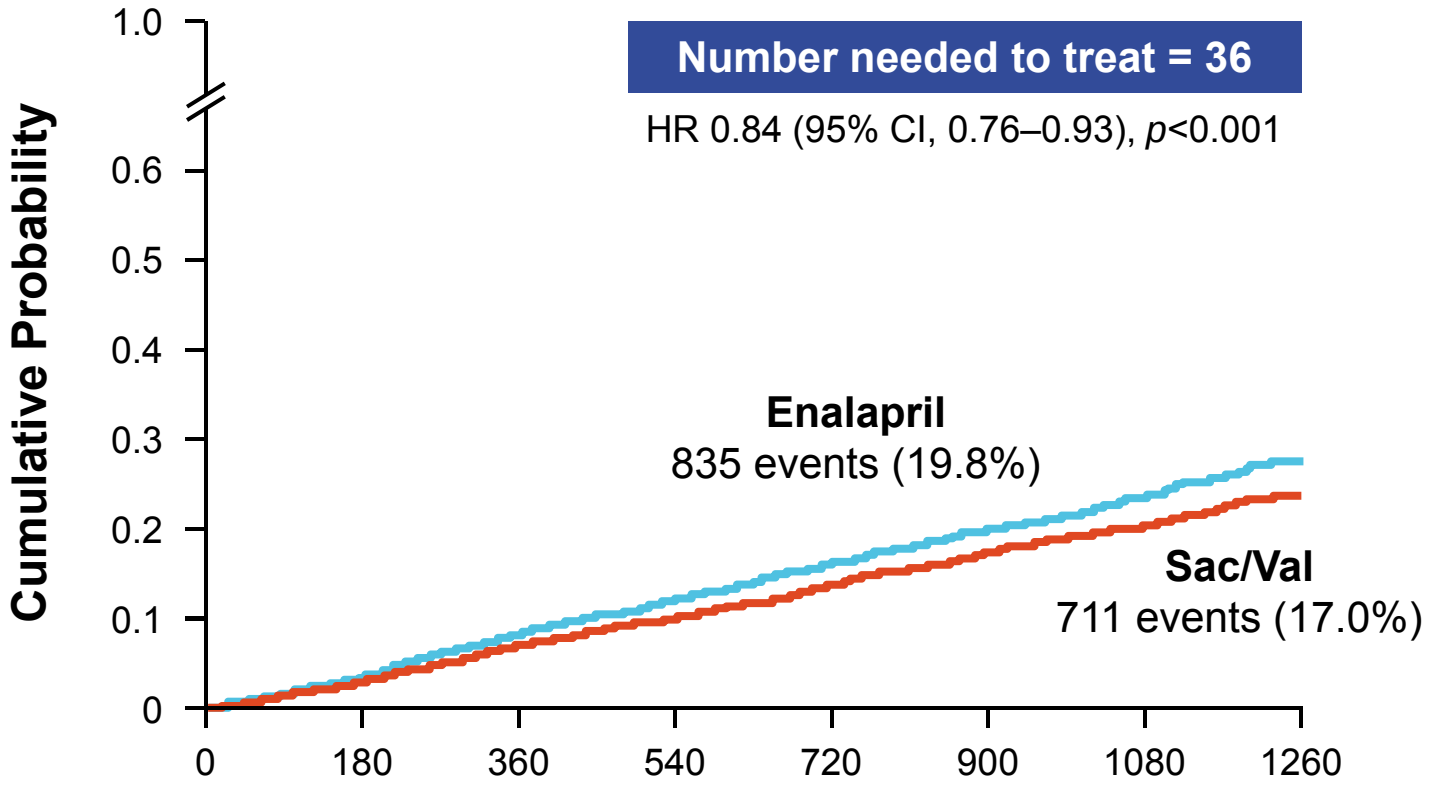
McMurray JJV, et al. *N Engl J Med.* 2014;371:993-1004.

Sac/Val vs. Enalapril on Primary Endpoint and on CV Death by Subgroups



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

PARADIGM-HF: All-Cause Mortality



Number at Risk								
Sac/Val	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

Sac/Val = Sacubitril/Valsartan.

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.

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 …

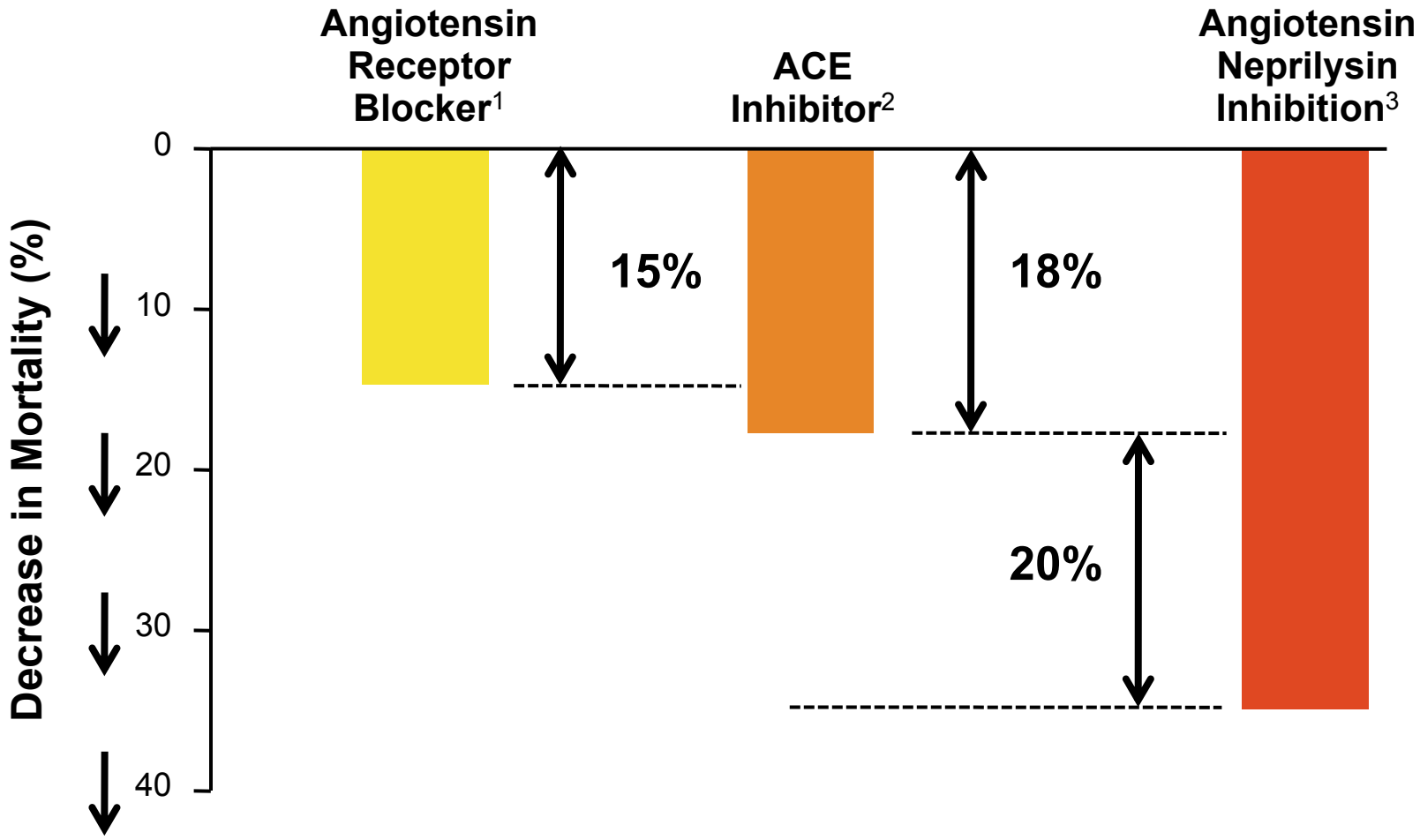
- Reducing the risk of CV death and HF hospitalization by incremental 20%
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- *Incrementally* improving symptoms and physical limitations

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

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

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



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.

New FDA-Approved Sacubitril/Valsartan

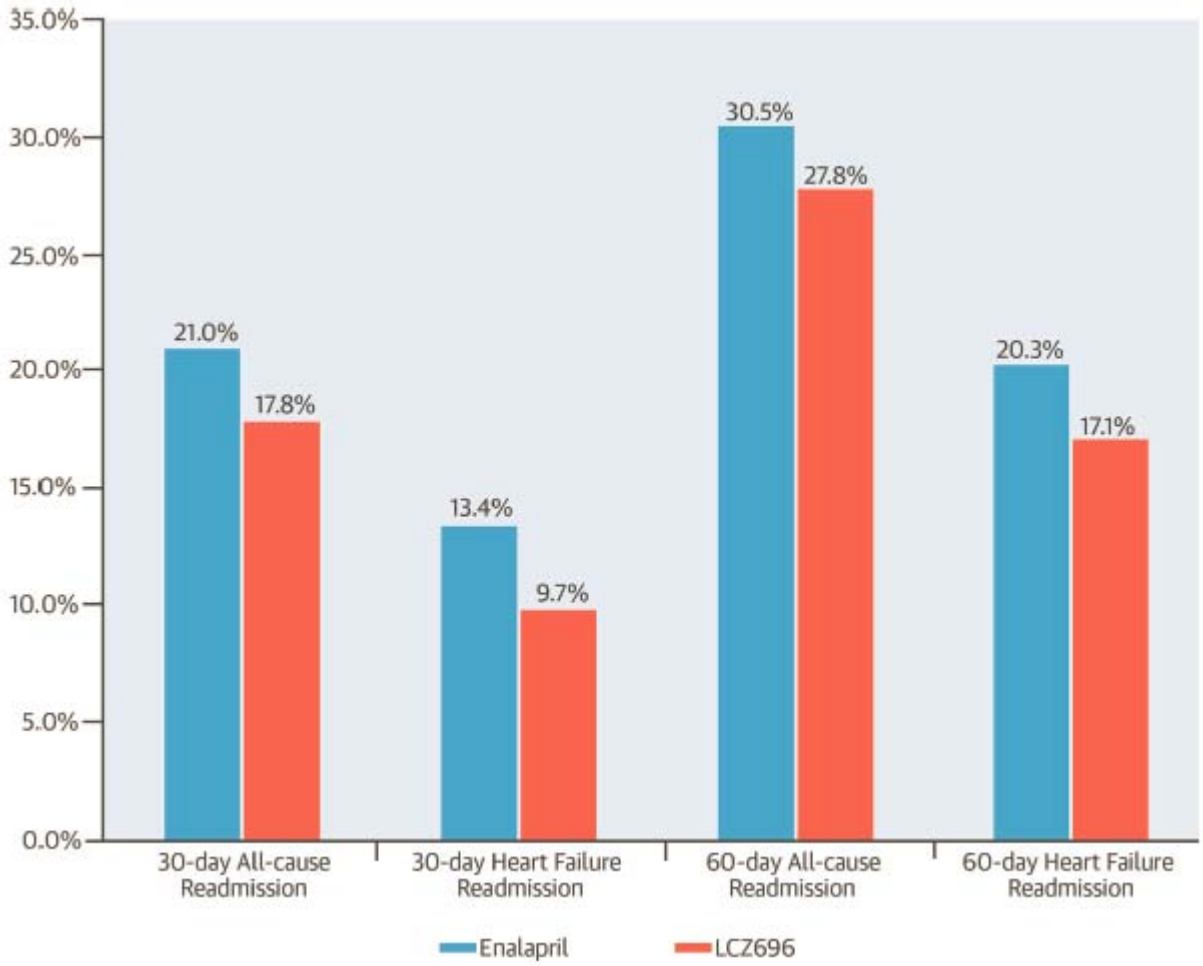
	Sacubitril/Valsartan
Brand name	Entresto
Indication	The fixed-dose combination of the neprilysin inhibitor sacubitril and the ARB valsartan is indicated to reduce the risk of CV death and HF hospitalization in patients with HF with reduced ejection fraction.
Dosage	Start with 49/51 mg twice daily. Double 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% Sac/Val vs. 0.2% Enalapril).

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

Practical Points on Use of Sacubitril/Valsartan

- Starting dose is 24/26 mg twice daily, unless patient is currently tolerating full dose ACEI or ARB in which case start 49/51 mg twice daily
- Target dose is 97/103 mg twice daily
- After 2-4 weeks uptitrate to next dose with ultimate goal to achieve target dose
- Monitor SBP, renal function and K as you would with ACEI or ARB use
- Space out dosing from other vasoactive medications if needed
- Adjust diuretics doses based on volume status

Influence of Sacubitril/Valsartan on Readmission Rates After HF Hospitalization: PARADIGM-HF



30 Day All Cause Readmission Odds Ratio: 0.74; 95% CI 0.56-0.97

30 Day HF Readmission Odds Ratio: 0.62; 95% CI 0.45-0.87

2,383 investigator-reported HF hospitalizations, of which 1,076 (45.2%) occurred in subjects assigned to sacubitril/valsartan and 1,307 (54.8%) occurred in subjects assigned to enalapril.

Desai, A.S. et al. J Am Coll Cardiol. 2016;68(3):241–8.

Efficacy of Sacubitril/Valsartan vs. Enalapril at Lower than Target Doses in HFrEF

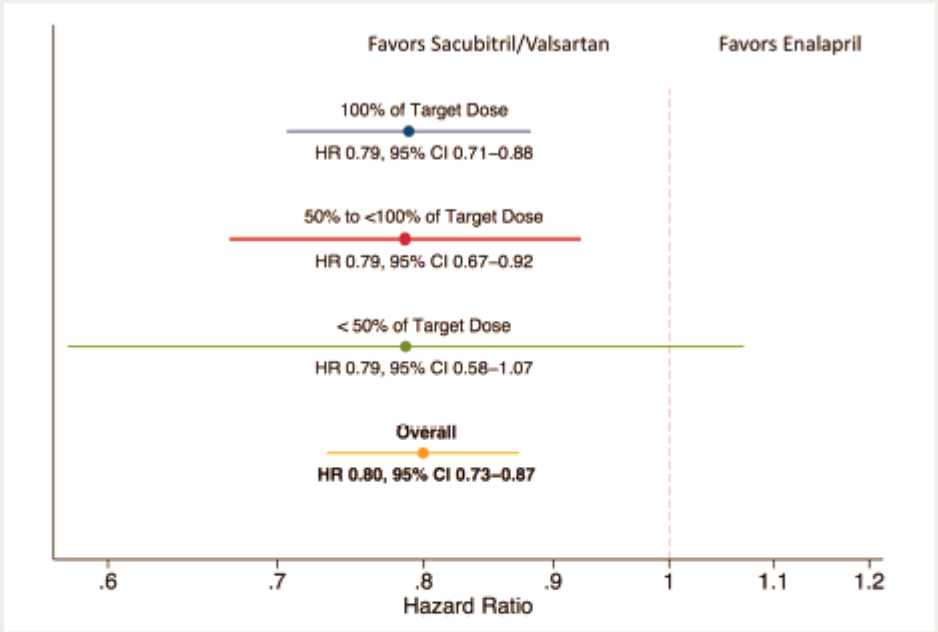


Figure 3 Hazard ratios (HR; sacubitril/valsartan relative to enalapril) of the primary outcome measure by time-updated mean dose post-randomization. Participants taking lower than target sacubitril/valsartan doses had a lower risk of the primary event compared with those taking lower than target doses of enalapril. CI, confidence interval.

In the two treatment arms, participants with a dose reduction (43% of those randomized to enalapril and 42% of those randomized to sacubitril/valsartan) had similar baseline characteristics and similar baseline predictors of the need for dose reduction.

However, the treatment benefit of sacubitril/valsartan over enalapril following a dose reduction was similar (HR 0.80, 95% CI 0.70–0.93, *P <0.001) to that observed in* patients who had not experienced any dose reduction (HR 0.79, 95% CI 0.71–0.88, *P <0.001)*

European Journal of Heart Failure (2016) doi:10.1002/ejhf.580

2016 ACC/AHA/HFSA Heart Failure Guideline Update

Pharmacological Treatment for Stage C HF*r*EF

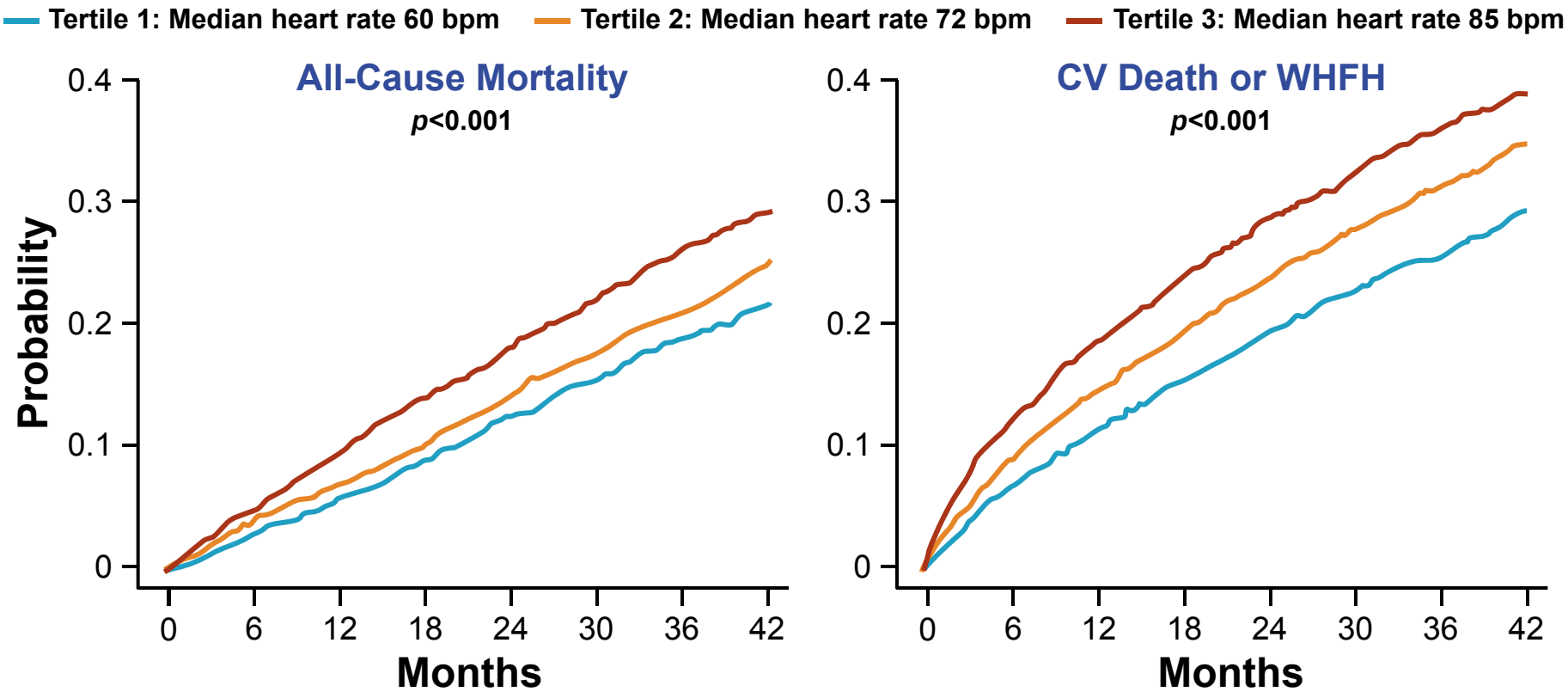
Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI		
COR	**LOE**	**Recommendations**
I	**ACE: A**	**The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)* (9-14), OR ARBs *(Level of Evidence: A)* (15-18), OR ARNI *(Level of Evidence: B-R)* (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.**
	ARB: A	
	ARNI: B-R	
I	**ARNI: B-R**	**In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).**
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 (31, 32).**
III: Harm	**C-EO**	**ARNI should not be administered to patients with a history of angioedema.**

ARNI = angiotensin receptor blocker and neprilysin inhibitor; COR = class of recommendation; LOE = level of evidence.

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

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.



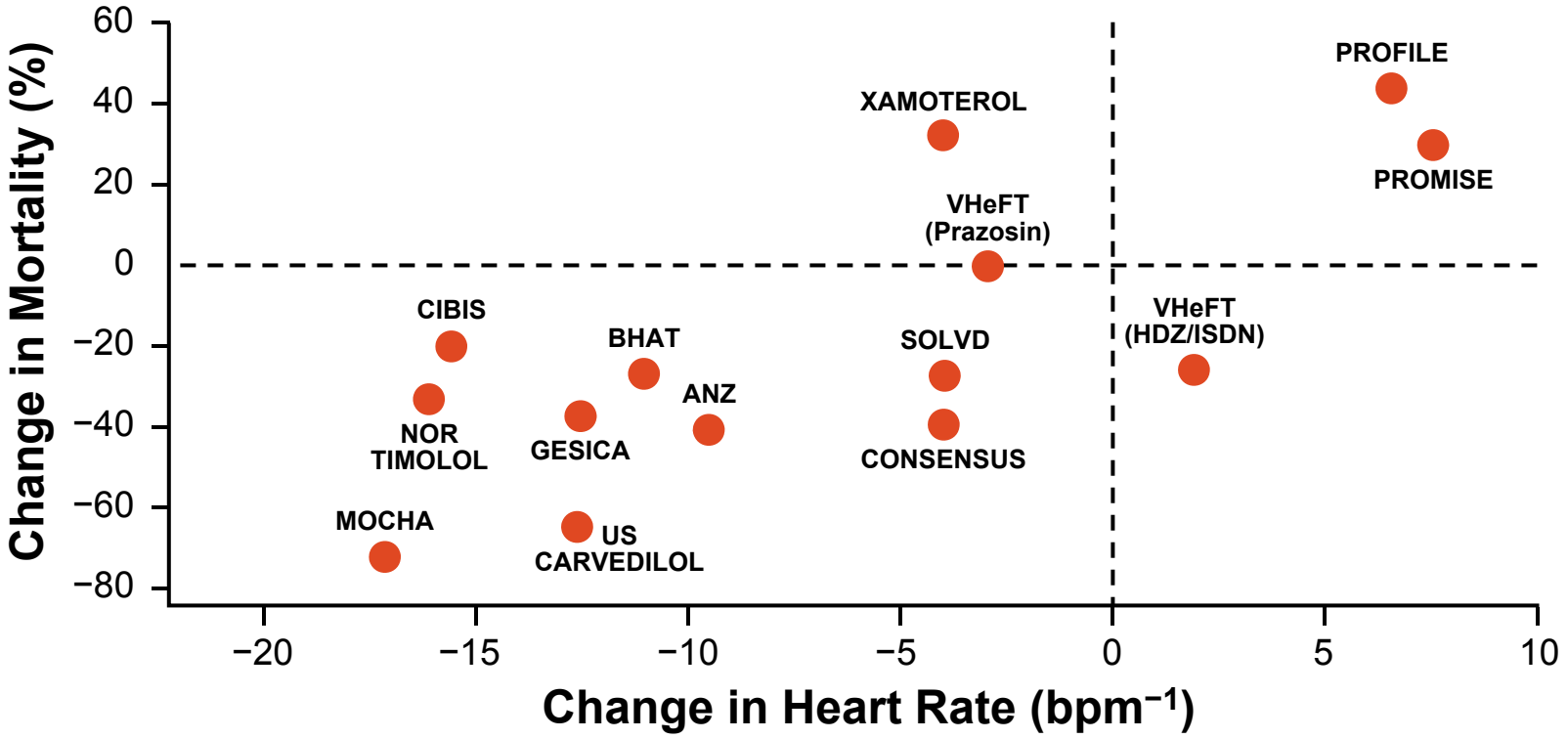
Heart rate is an important predictor of mortality and CV outcomes in patients with HF

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.

Change in Heart Rate and Mortality Observed in Heart Failure Trials

Relationship between changes in heart rate and mortality in studies of chronic heart failure



HF trials with both beta-blocker and non-beta-blocker treatment demonstrate a relationship between a change in heart rate and the risk of mortality in HF

Adapted from: Kjekshus J, et al. *Eur Heart J*. 1999;1(suppl H):H64-H69.

Beta-Blocker Dose and Heart Rate Reduction in Patients with Chronic Heart Failure

Meta-analysis of 17 randomized trials in subjects with HF to examine whether the beta-blocker dose or the magnitude of heart rate reduction could account for differences in treatment effects among HF beta-blocker trials, 1966–2008.

Potential Modifier	# Trials	# Subjects	Ratio of Relative Risks (95% CI)	*p*-Value
Heart rate reduction	17	17,831	0.82 (0.71–0.94) per 5 bpm	0.006
Beta-blocker dose	17	17,660	1.02 (0.93–1.10) per increment	0.69
Baseline heart rate	19	17,981	1.07 (0.88–1.32) per 5 bpm	0.47

Results of univariable meta-regressions evaluating the effect of individual covariates on the potential mortality benefits of beta-blockers in HF

McAlister FA, et al. *Ann Intern Med*. 2009;150:784-794.

Regulating Heart Rate: Voltage-Gated Ion Current

The activation of voltage-dependent channels helps drive sinus node automaticity during diastole

Major Currents Involved in Sinus Node Automaticity

I_f (funny current)

- Specific to sinus node automaticity
  - Hyperpolarization-activated current
  - Carried by Na^+/K^+ in the SA node
  - Phase 4 depolarization generated
  - Automaticity of the pacemaker cells initiated

$I_{ca,T}$ (T-type Ca^{2+} currents)

- Specific to sinus node automaticity
  - May contribute to the inward current to the later phase 4 depolarization in pacemaker cells
  - May contribute to the action potential propagation in AV nodal cells

$I_{ca,L}$ (L-type Ca^{2+} currents)

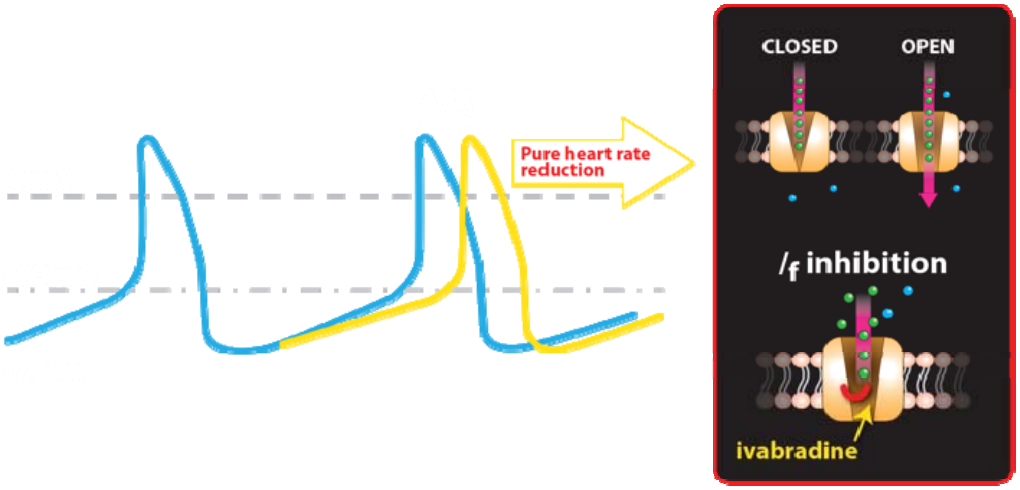
- Specific to sinus node automaticity
  - Responsible for phase 0 depolarization and propagation in SA and AV nodal tissue
  - Main trigger of Ca^{2+} release from sarcoplasmic reticulum (Ca^{2+}-induced Ca^{2+} release)

SA = sinoatrial.

Adapted from: Rubart M, et al. In: Libby P, et al., eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th ed. Philadelphia, PA: Saunders Elsevier. 2008:Chap 31.

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.

Objective of the SHIFT Study

To evaluate whether the I_f inhibitor ivabradine improves cardiovascular outcomes in patients with:

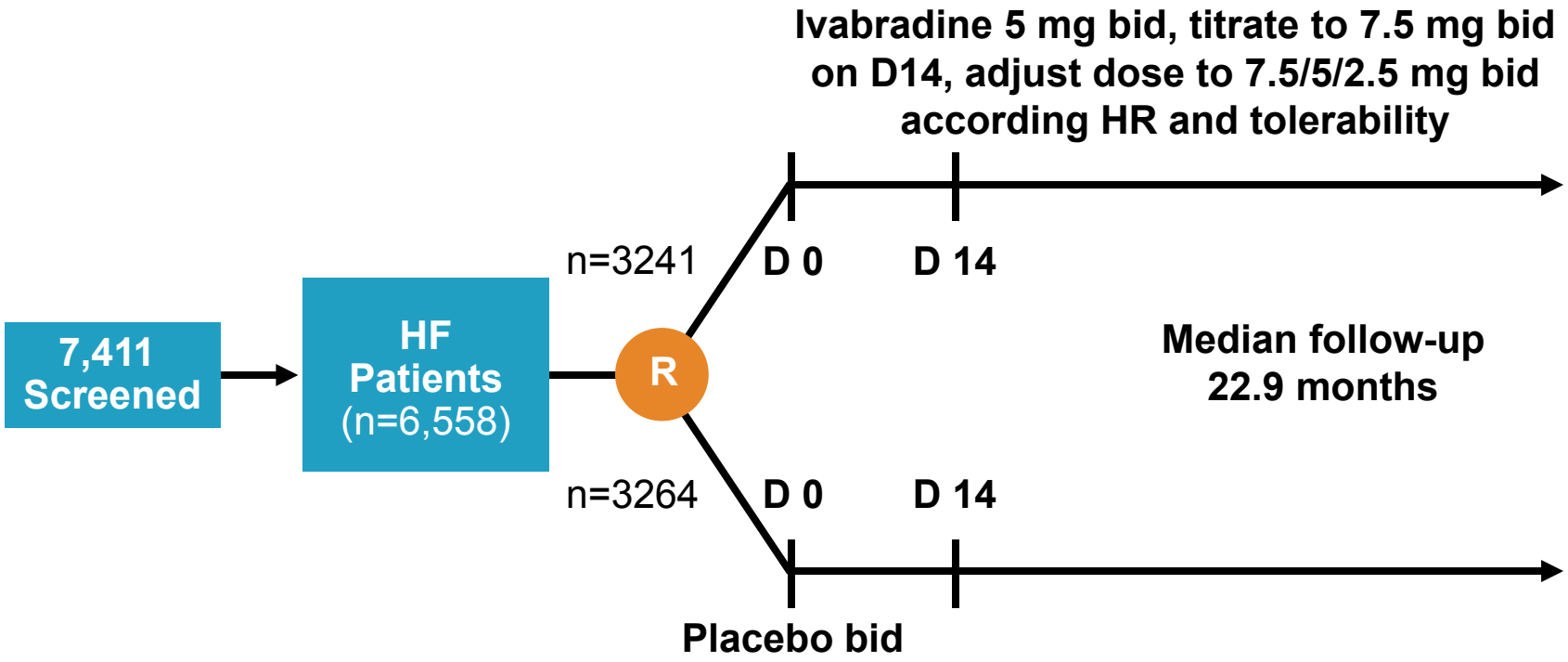
1. Moderate to severe chronic HF
2. Left ventricular EF ≤35%
3. Heart rate ≥70 bpm, and
4. Recommended therapy

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

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

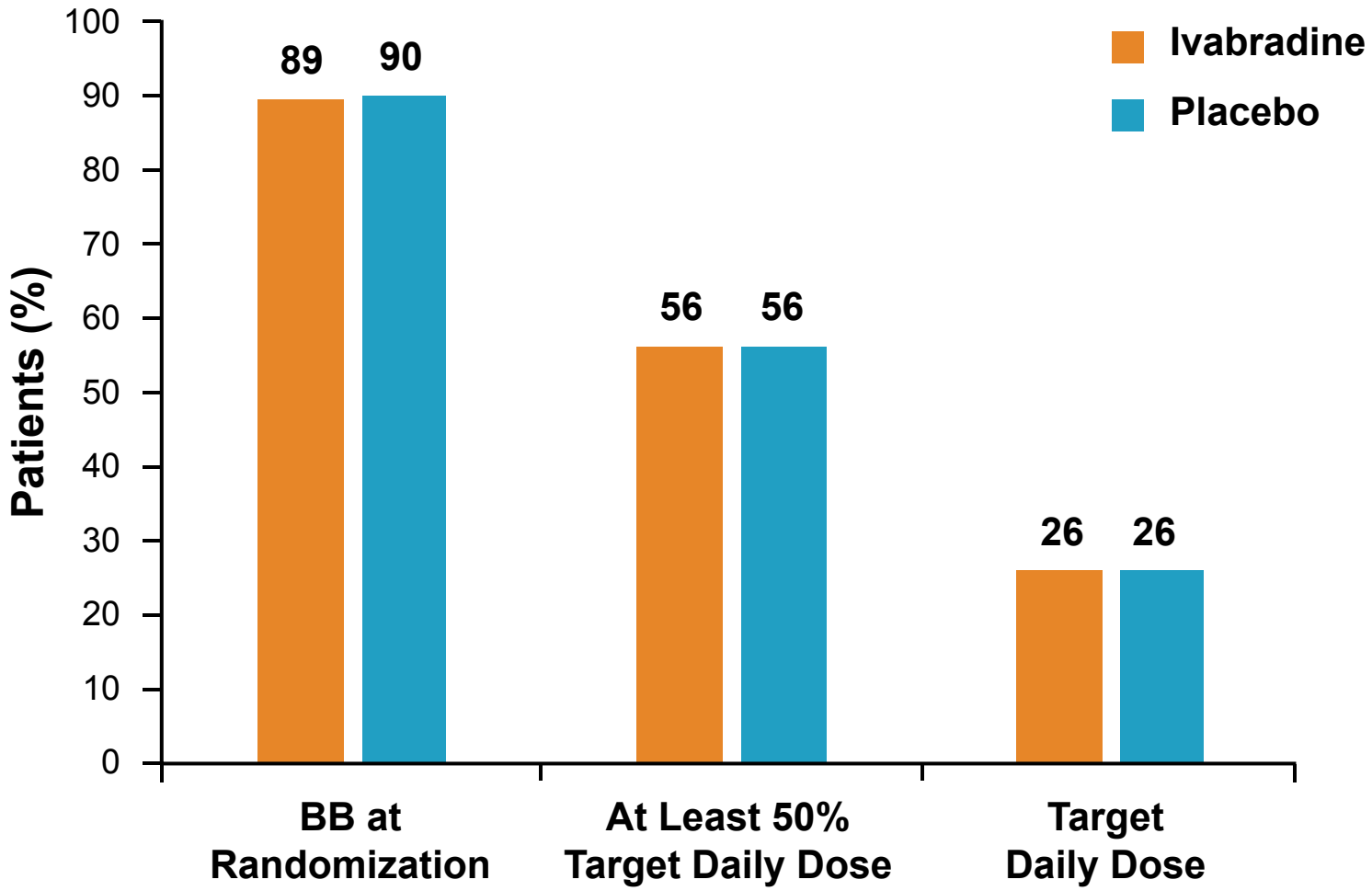
Swedberg K, et al. *Lancet*. 2010;376:875-885.

SHIFT Study: Baseline Characteristics

	Ivabradine (n=3241)	Placebo (n=3264)
Mean heart rate (bpm)	79.7	80.1
Mean LVEF (%)	29.0%	29.0%
NYHA Class II/III (%)	49%/50%	49%/50%
Mean SBP, mm Hg	122.0	121.4
eGFR, mL/min/1.73 m^2	74.6	74.8
Beta-blocker (%)	89%	90%
ACE inhibitor/ARB (%)	79%/14%	78%/14%
Diuretics (%)	84%	83%
Aldosterone antagonist (%)	61%	59%
Digitalis (%)	22%	22%
CRT/ICD (%)	1%/3%	1%/4%

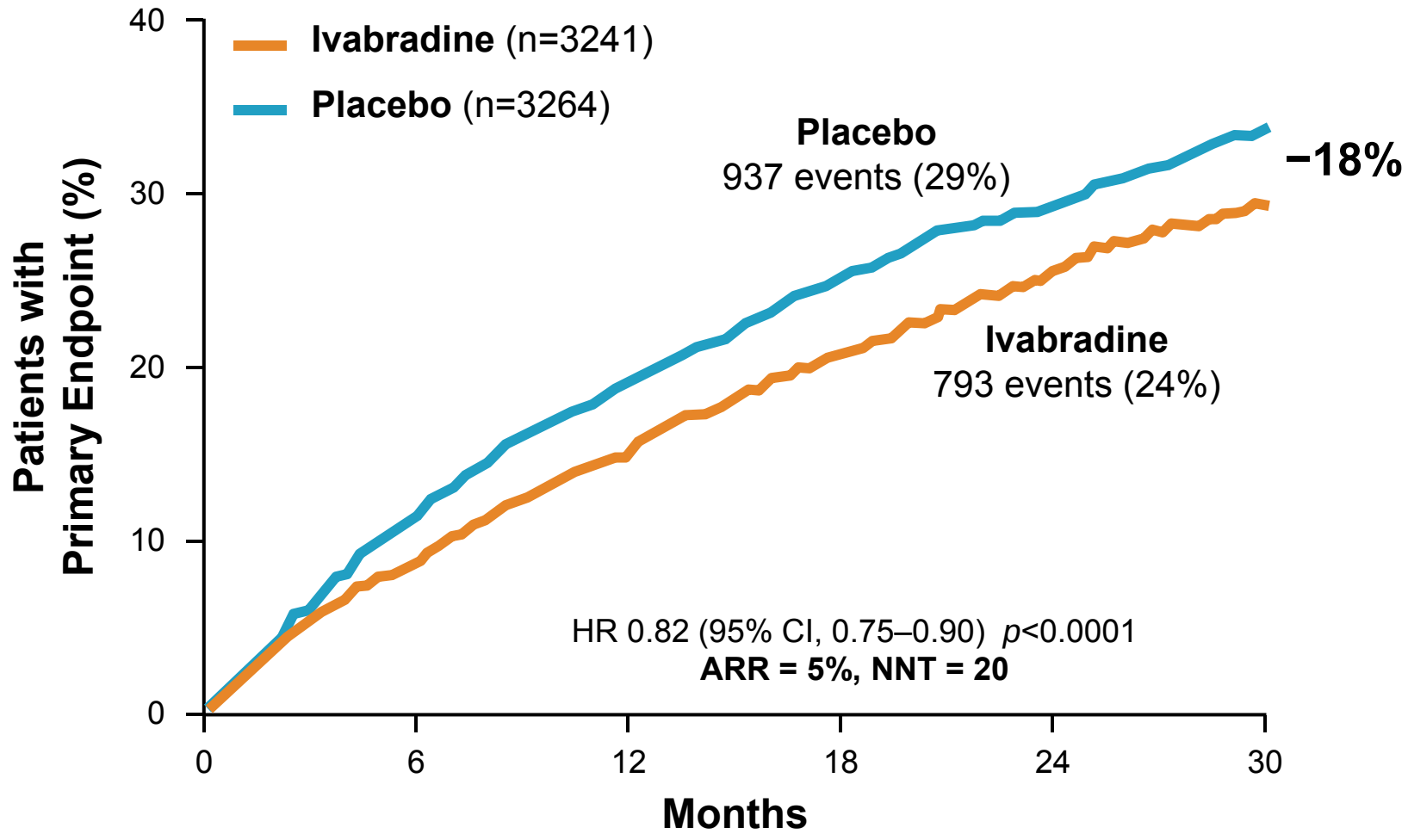
Swedberg K, et al. *Lancet*. 2010;376:875-885.

Background Beta-Blocker Treatment



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

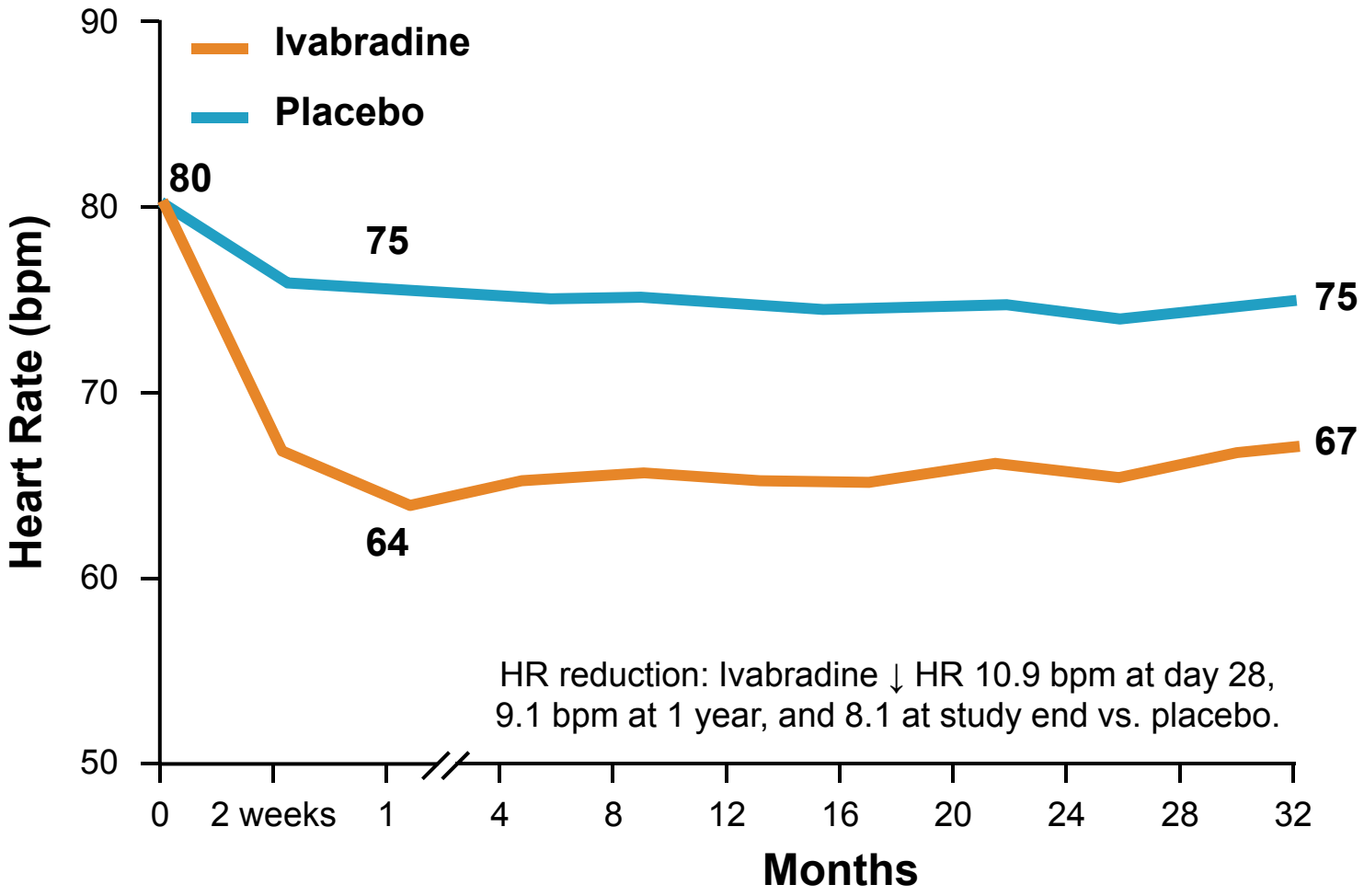
SHIFT Study: Primary Endpoint of CV Death or Hospitalization for Worsening HF



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

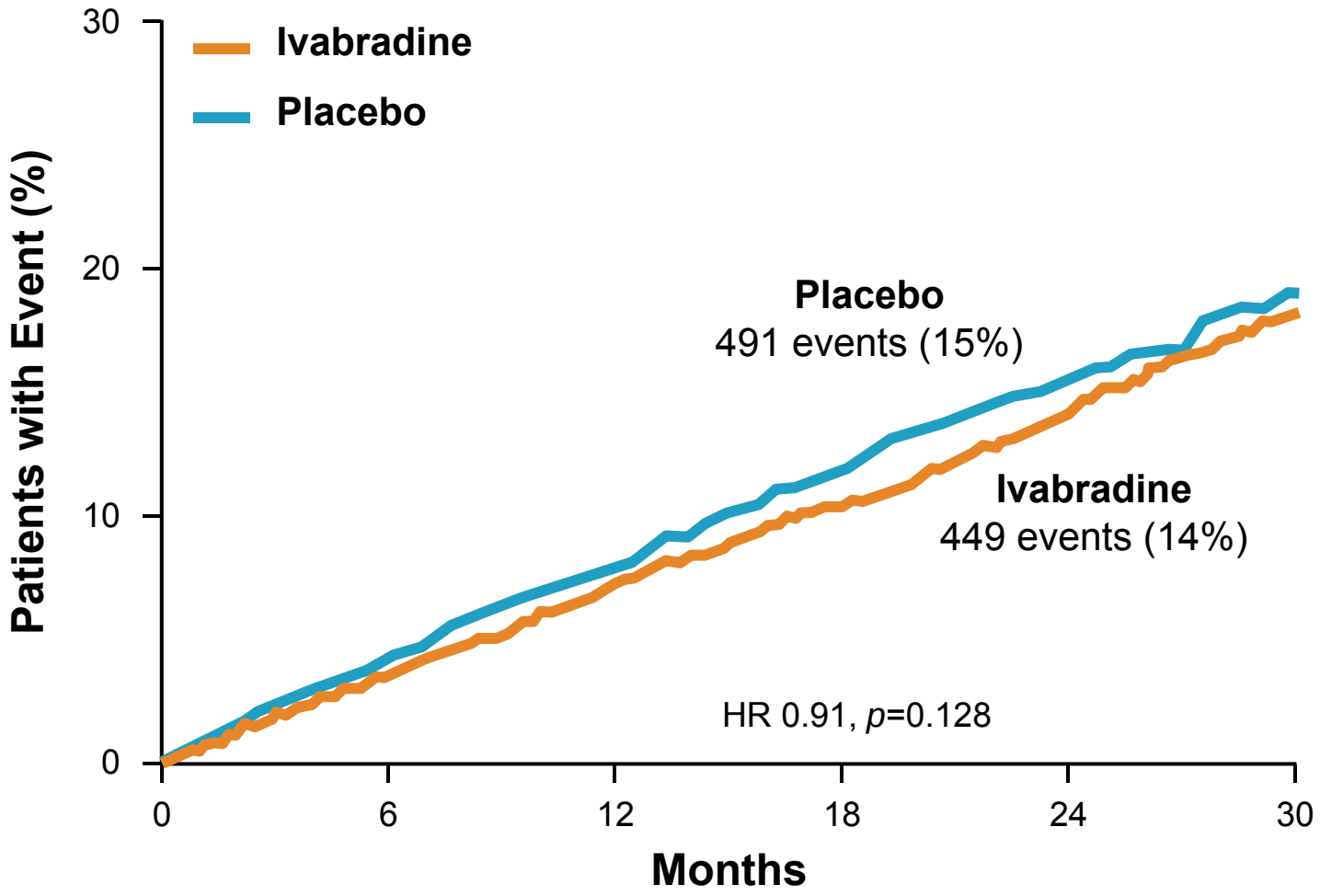
SHIFT Study: Mean Heart Rate

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



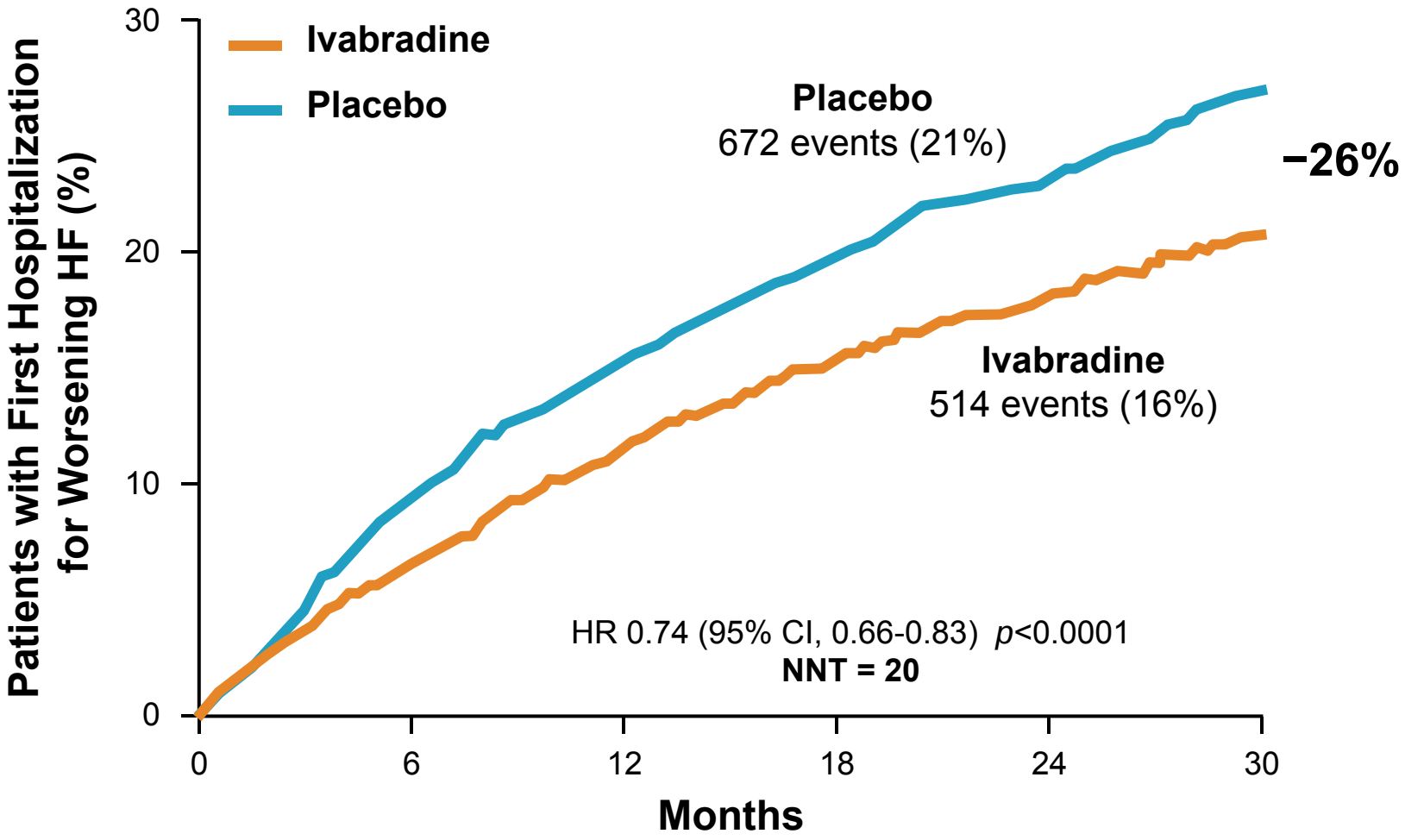
Swedberg K, et al. *Lancet*. 2010;376:875-885.

SHIFT Study: Cardiovascular Death



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

SHIFT Study: Hospitalization for Worsening HF



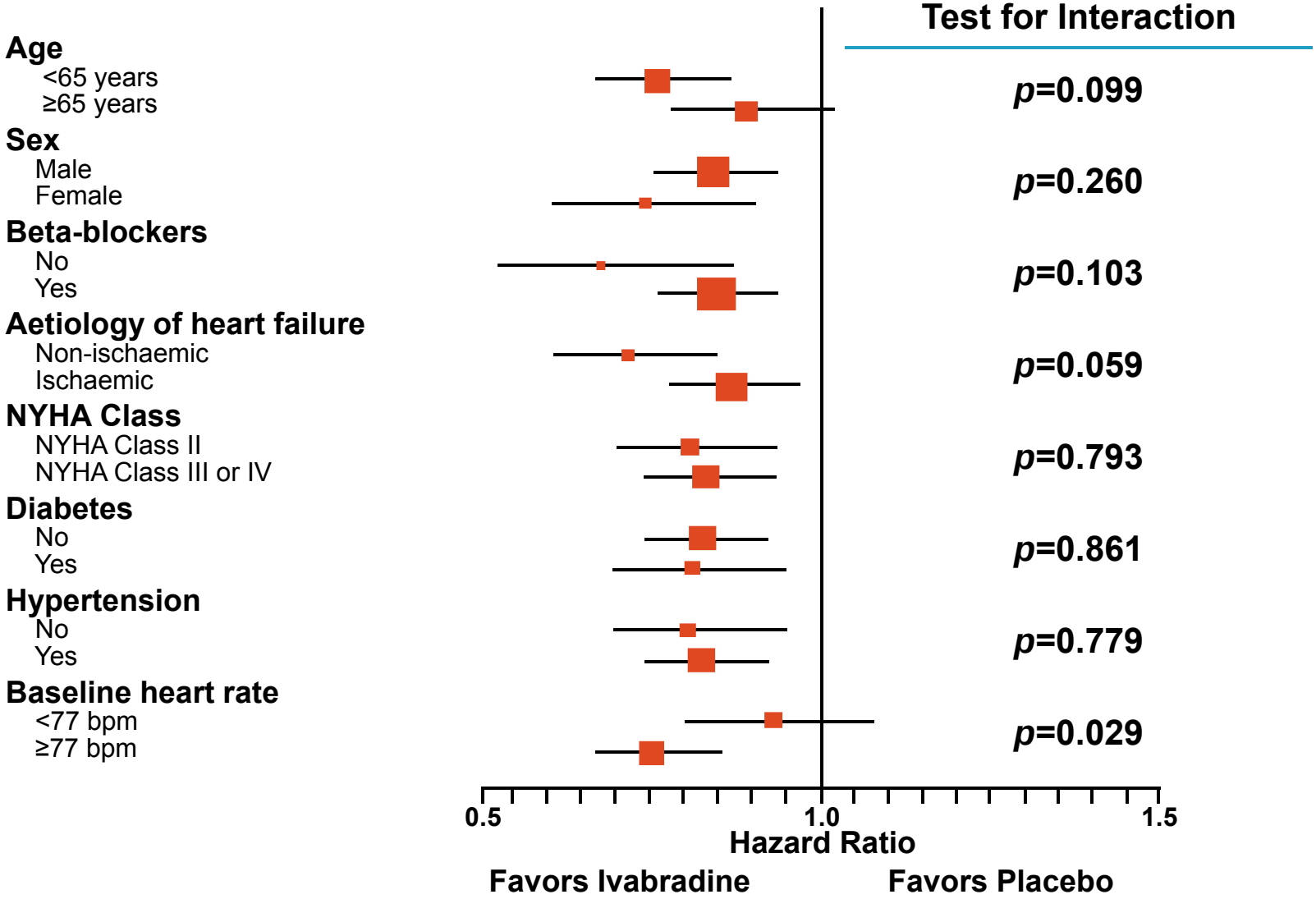
Swedberg K, et al. *Lancet*. 2010;376:875-885.

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

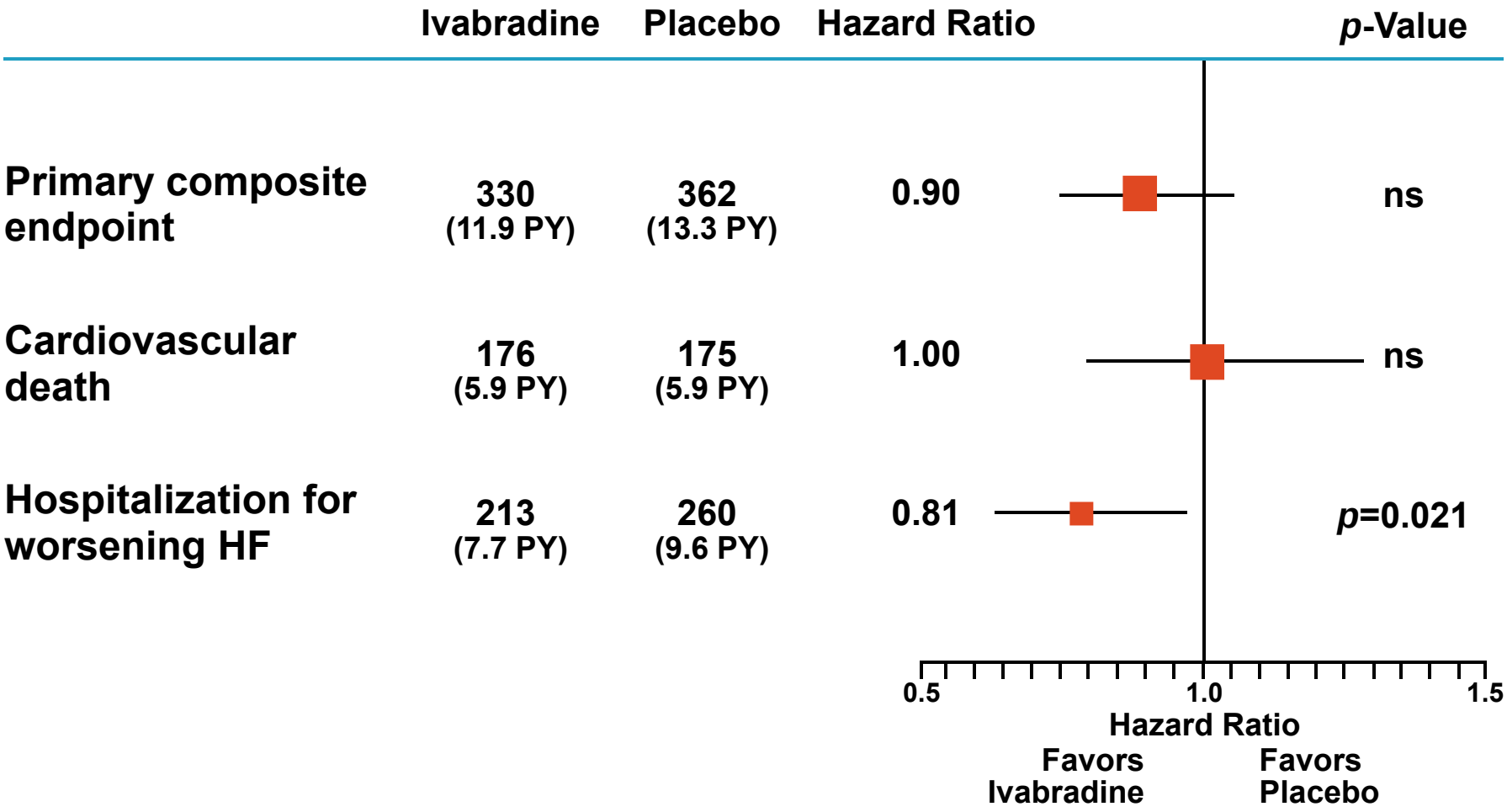
Swedberg K, et al. *Lancet*. 2010;376:875-885.

SHIFT Study: Effect of Ivabradine in Prespecified Subgroups



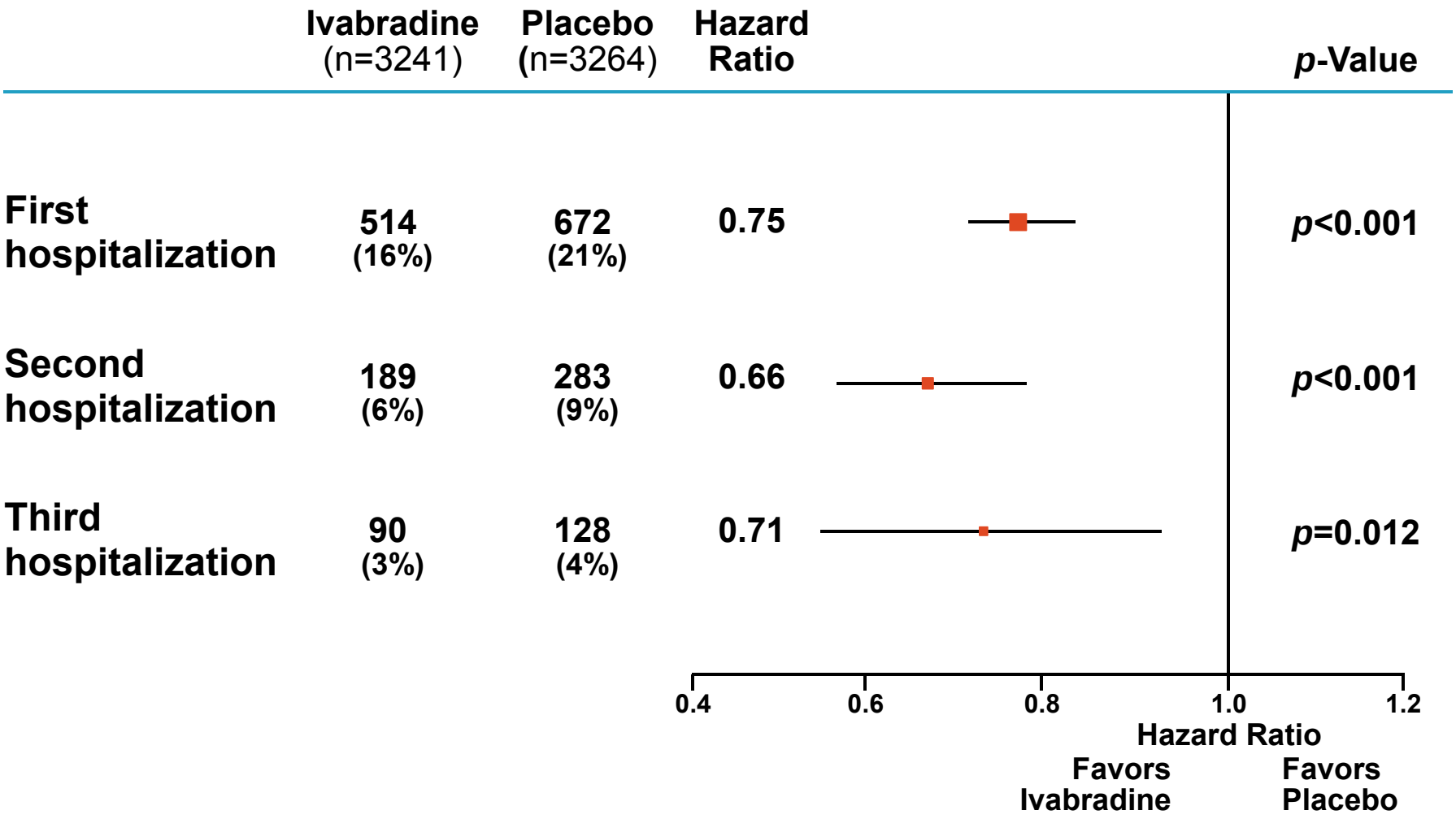
Swedberg K, et al. *Lancet*. 2010;376:875-885.

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



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

SHIFT Study: Effect on Recurrence of Hospitalizations for Worsening HF



Broer JS, et al. *Eur Heart J*. 2012;33(22):2813-2820.

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**

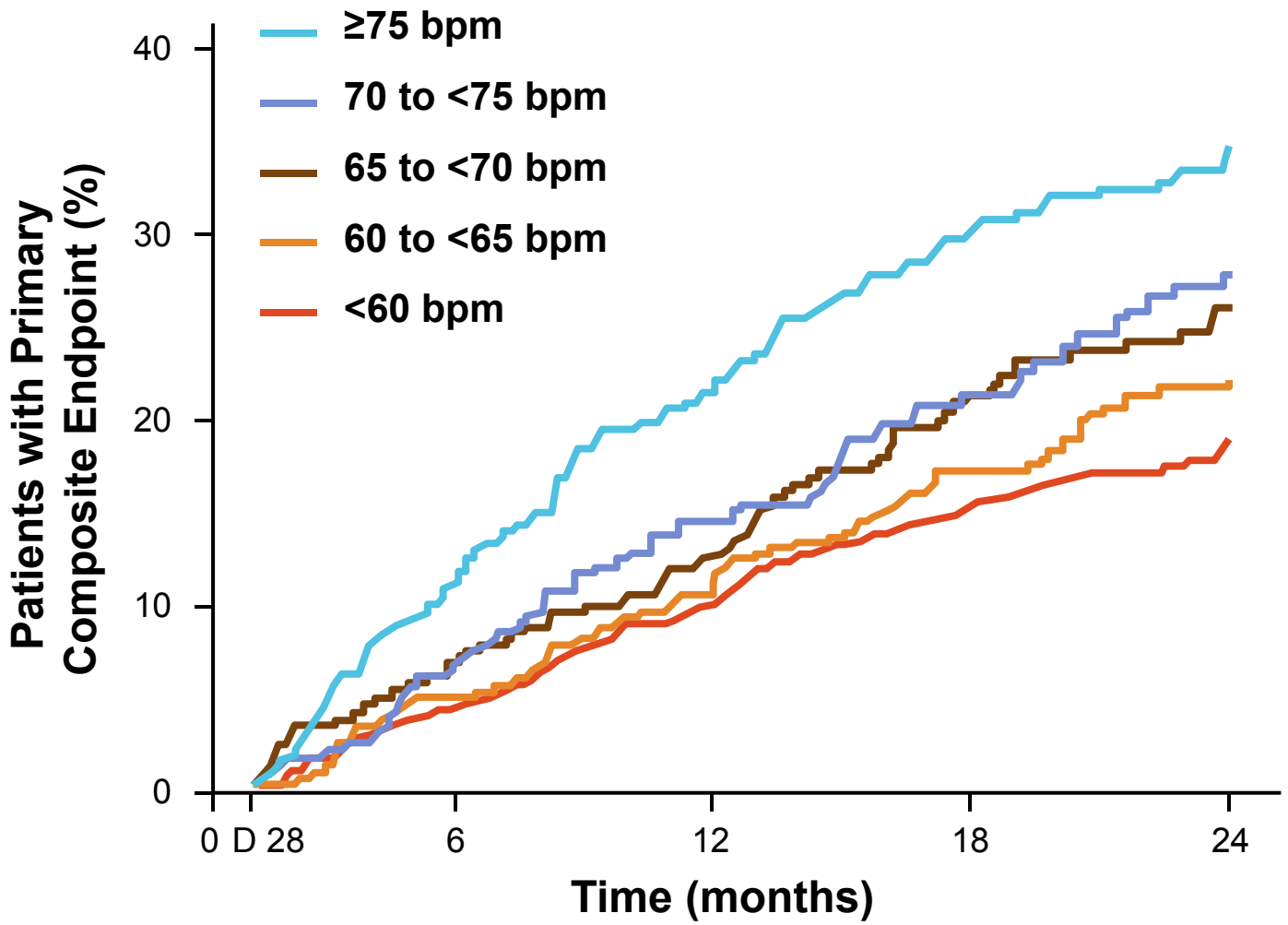
Phosphenes are luminous phenomena; bradycardia is defined here as resting heart rate was lower than 50 bpm or the patient had signs or symptoms related to bradycardia.

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

Summary of SHIFT Study

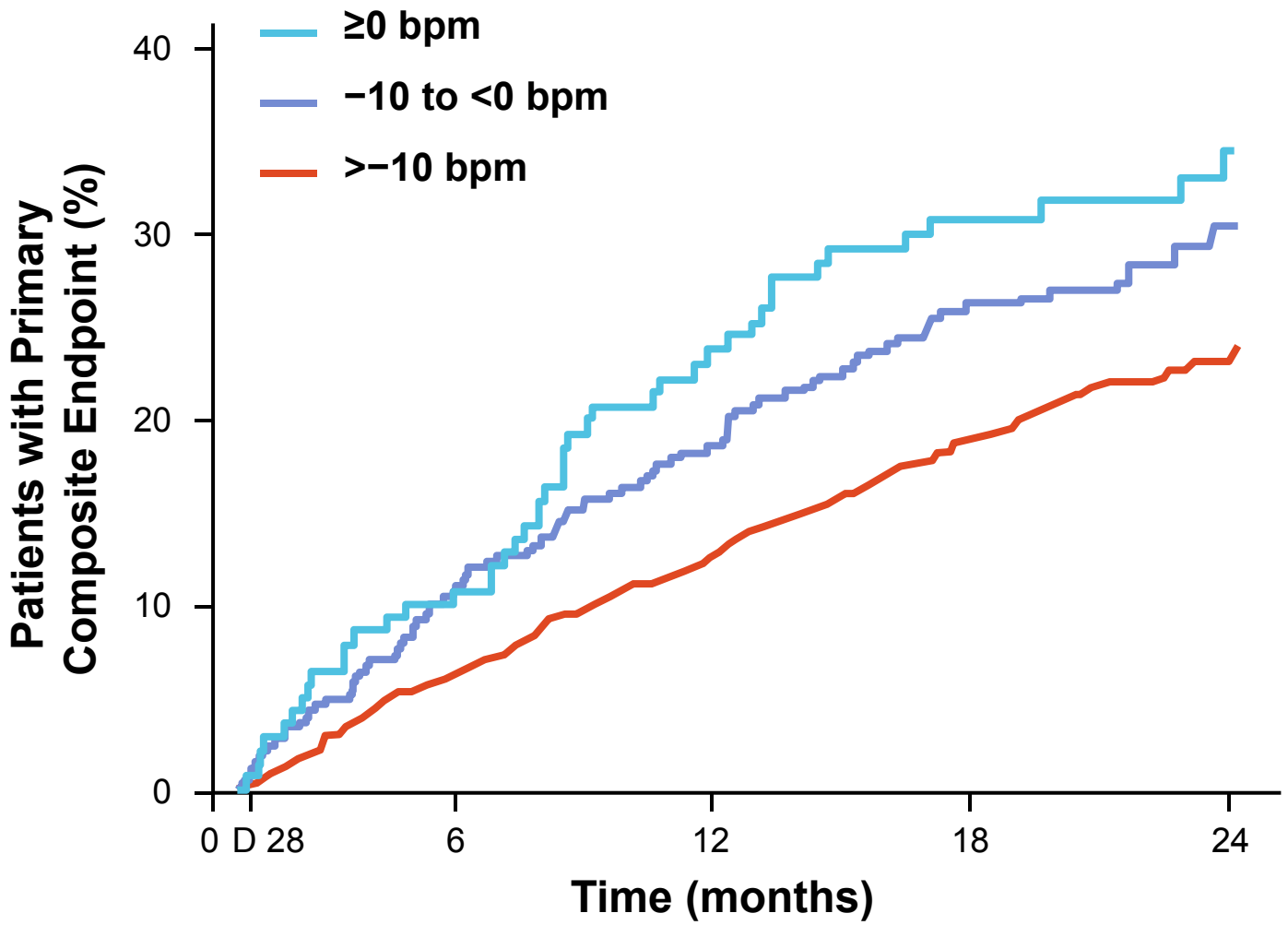
- HFrEF + elevated HR is associated with poor outcomes
  - Primary composite endpoint with placebo = 18%/yr
- Ivabradine reduced CV death or hospitalization for worsening heart failure by 18%
  - ARR = 5%; NNT = 20
- This beneficial effect was driven mainly by a favorable effect on HF death/admission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

Effect of Ivabradine on Outcomes according to HR Achieved at 28 Days



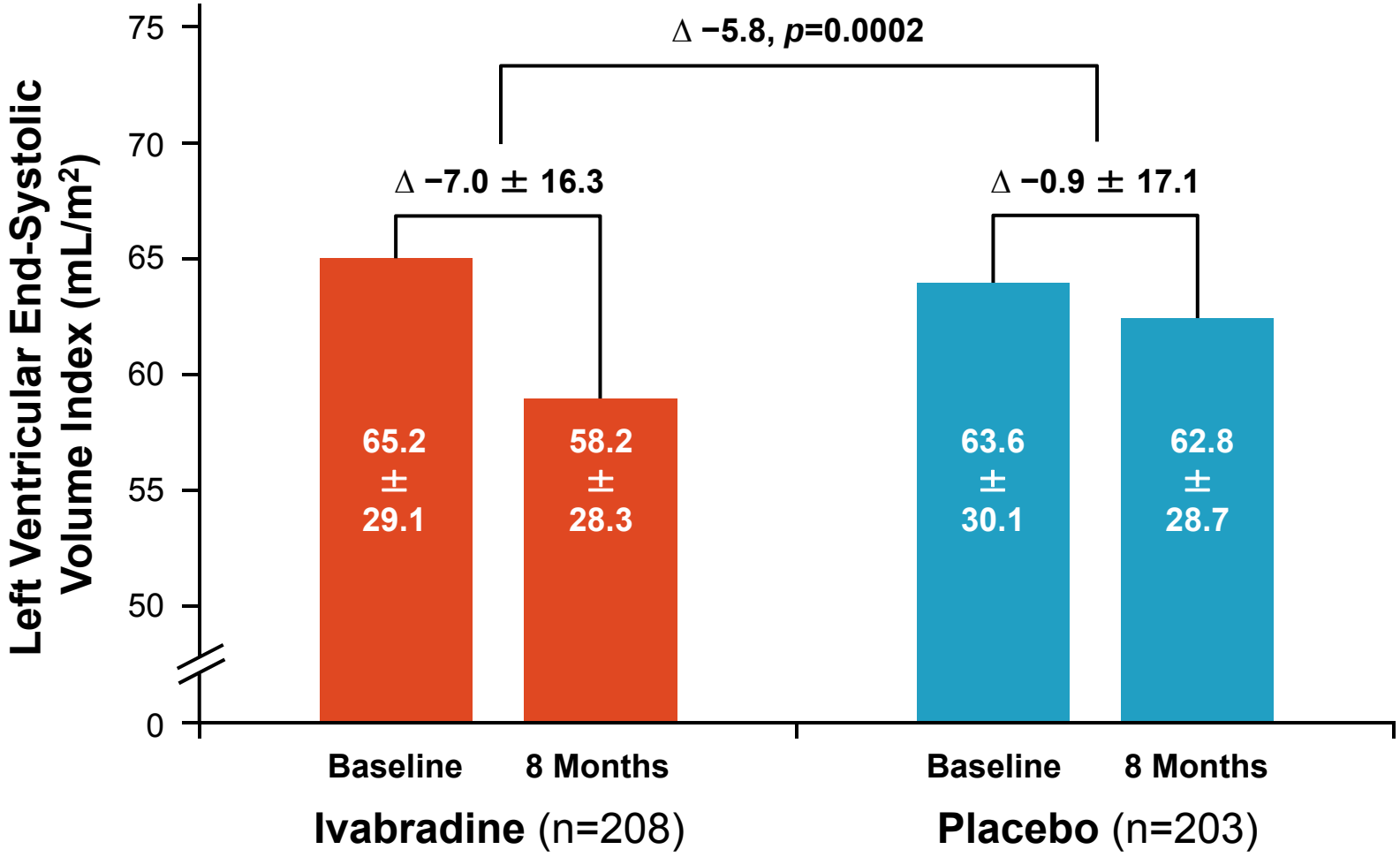
Böhm M, Borer J, Ford I, et al. *Clin Res Cardiol.* 2013;102(1):11-22.

Effect of Ivabradine on Outcomes according to Magnitude of HR Reduction



Böhm M, Borer J, Ford I, et al. *Clin Res Cardiol.* 2013;102(1):11-22.

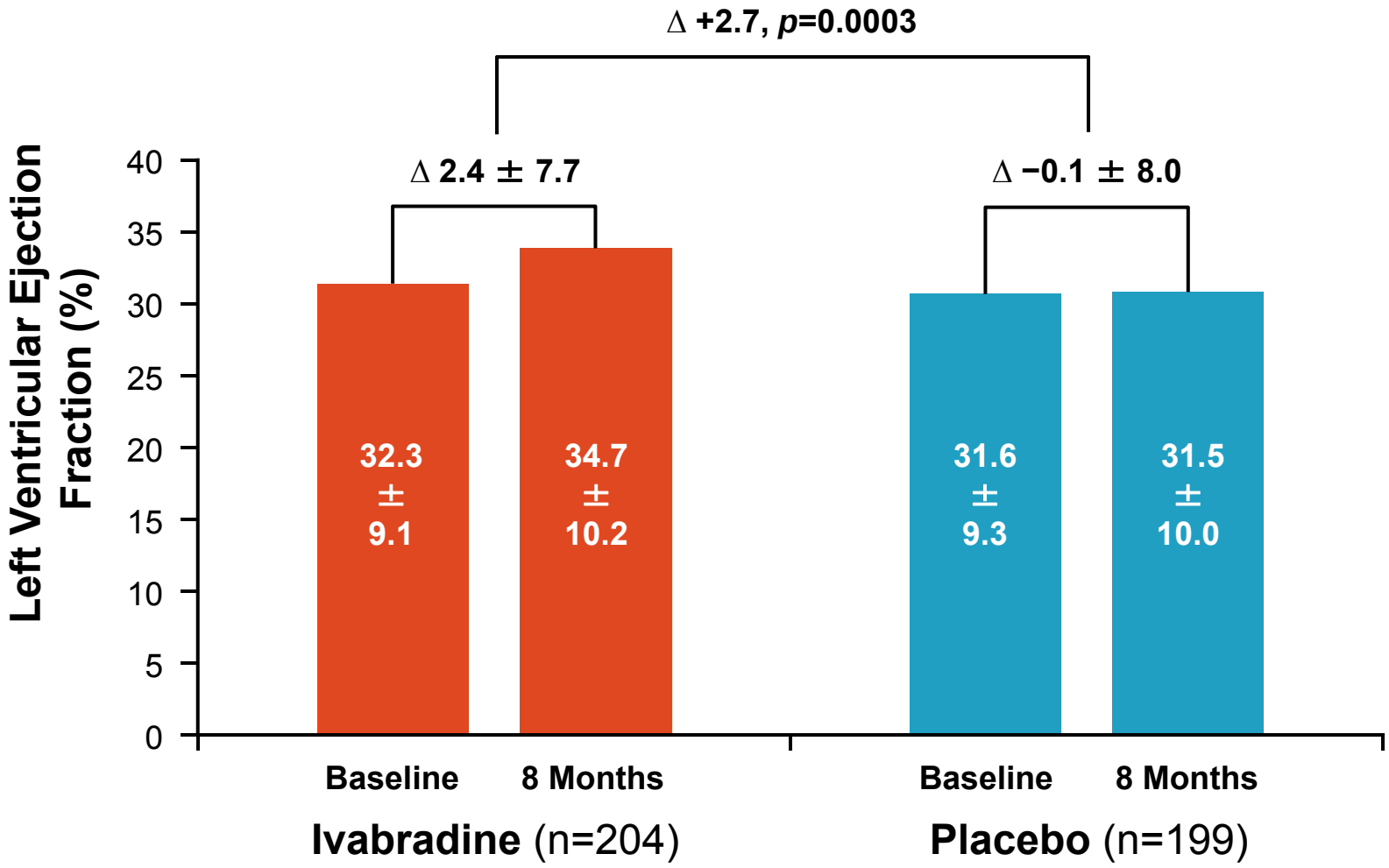
SHIFT Echo Substudy: Change in LVESVI from Baseline to 8 mos (Primary Endpoint)



LVESVI = left ventricular end-systolic volume index.

Tardif JC, et al. *Eur Heart J.* 2011;32(20):2507-2515.

SHIFT Echo Substudy: Change in LVEF from Baseline to 8 mos (Secondary Endpoint)



LVESVI = left ventricular end-systolic volume index.

Tardif JC, et al. *Eur Heart J*. 2011;32(20):2507-2515.

Pooled Analysis of BEAUTIFUL and SHIFT

Reduced EF, Heart Rate ≥ 75 bpm (N=7632)

	HR (95% CI)	*P*-value
CV mortality or hospitalization for HF	0.82 (0.75–0.90)	<0.0001
CV mortality	0.88 (0.78–1.00)	0.049
Hospitalization for HF	0.78 (0.70–0.87)	<0.0001
Total mortality	0.89 (0.80–1.00)	0.048

Fox K. Eur Heart J. 2013

FDA-Approved Ivabradine

	Ivabradine
Brand name	Corlanor
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 maximally 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.

Practical Points on Use of Ivabradine

- Starting dose is 5 mg twice daily
- Target HR is 50-60 bpm
- After 2 weeks:
  - If HR >60 bpm:
    Increase dose to 7.5 mg twice daily (Max dose)
  - If HR 50-60 bpm:
    Maintain initial dose
  - If HR <50 bpm or symptomatic bradycardia:
    Lower dose to 2.5 mg twice daily
  - If HR <50 bpm or symptomatic bradycardia and dose is 2.5 mg twice daily: Discontinue

2016 ACC/AHA/HFSA Heart Failure Guideline Update

Pharmacological Treatment for Stage C HF*r*EF

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

COR = class of recommendation; LOE = level of evidence.

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

Evidence-Based HFrEF 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%
ARNI	16%	36 over 27 months	27	21%
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
Ivabradine	NA	NA	NA	26%

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

Potential Impact of Optimal Implementation of Evidence-Based HFrEF 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)
ARNI (replacing ACEI/ARB)	2,287,296	2,287,296 (100)	28,484	(18,230-41,017)

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030. and JAMA Cardiology 2016

Advances in the Treatment of HF

- Increased attention to prevention
- ACEI/beta-blocker/aldosterone antagonist combination previously established as the “cornerstone” of therapy
- ARNI further reduces morbidity and mortality
- Evidence that beta-blockers’ effects are not homogeneous
- Ivabradine further reduces HF hospitalization risk
- 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