PIONEER-HF TRIAL FINDINGS AND SIGNIFICANCE

FEBRUARY 26, 2019

Presenter:

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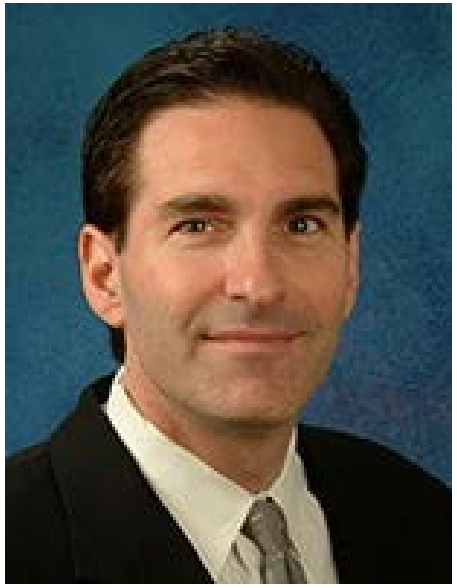
PRESENTER



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

American Heart Association.

Scope of Heart Failure

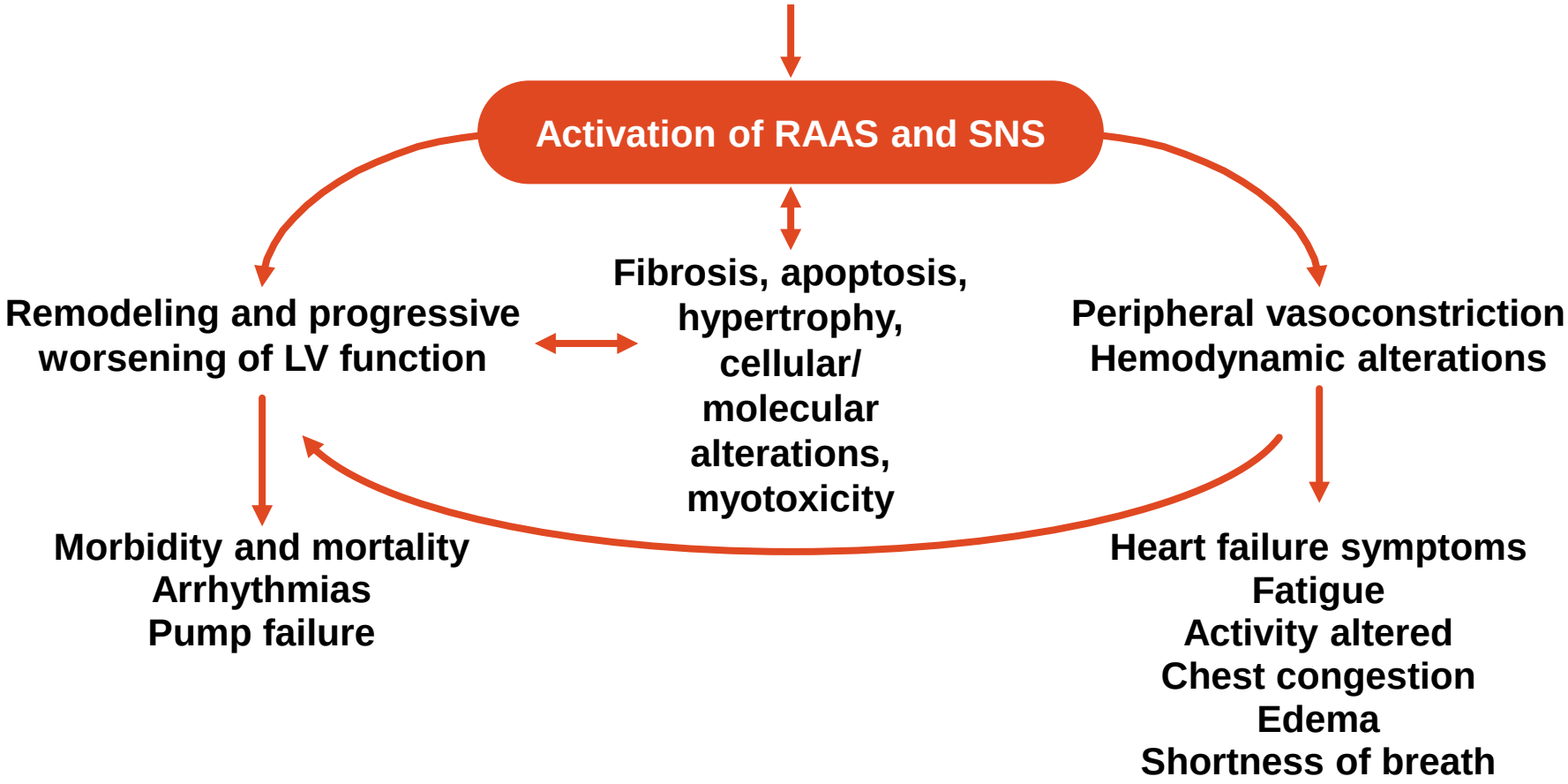
Prevalence	Incidence	Mortality	Hospital Discharges	Cost
6,500,000	1,000,000	308,976 (50% at 5 years)	900,000	$30.7 billion

- Heart failure (HF) is a major public health problem resulting in substantial morbidity, mortality, and healthcare expenditures
- Despite available effective treatments, a large number of eligible patients are not receiving optimal care
- Even with conventional therapy patients remain at risk for disease progression and adverse outcomes

American Heart Association. *2018 Heart and Stroke Statistical Update.* Dallas, Tex: American Heart Association; 2018

Neurohormonal Activation in Heart Failure

Myocardial injury to the heart (CAD, HTN, CMP, valvular disease)
Initial fall in LV performance, ↑ wall stress



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

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

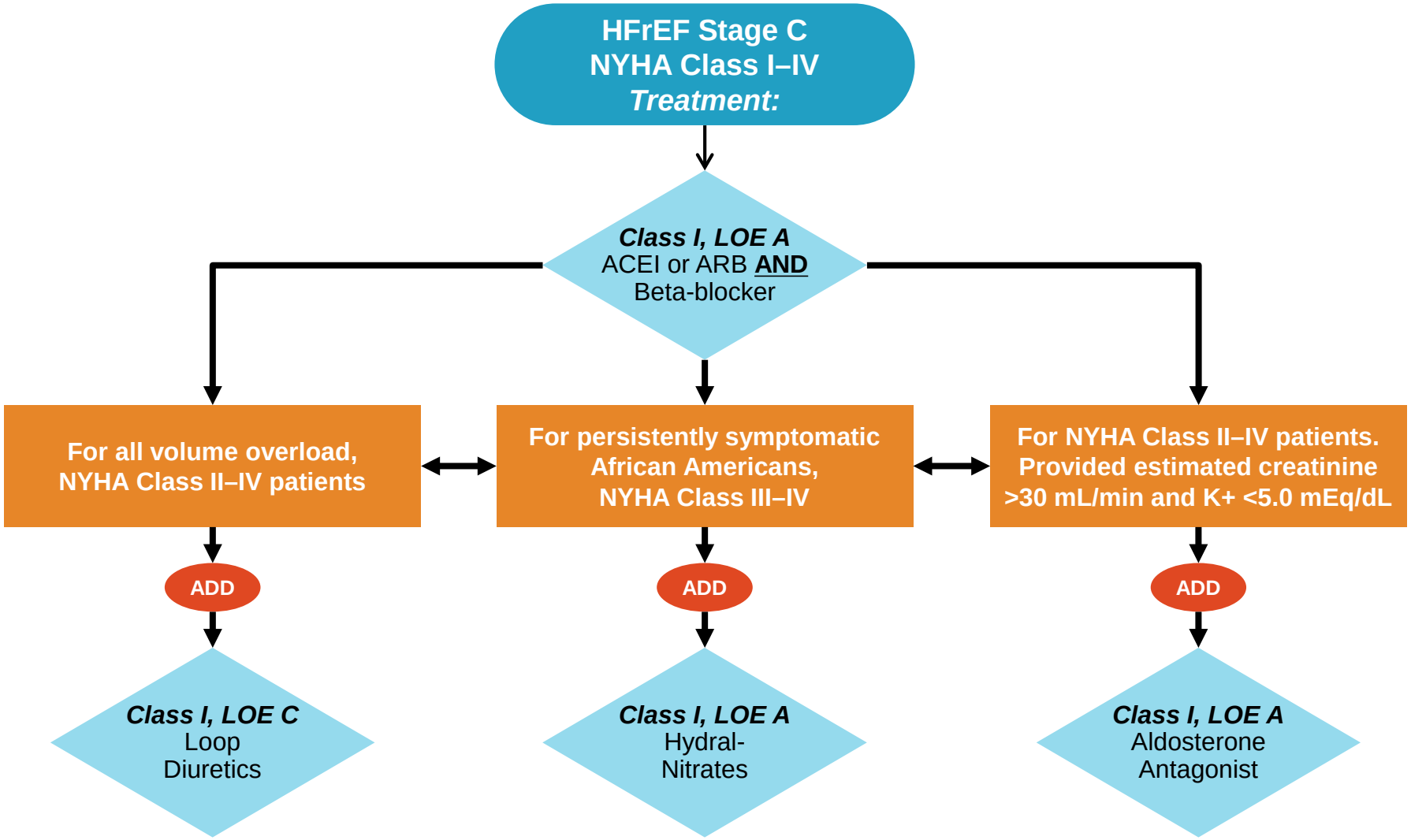
ACC/AHA HF Guidelines 2013:
Management of HFrEF (Stage C)

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.

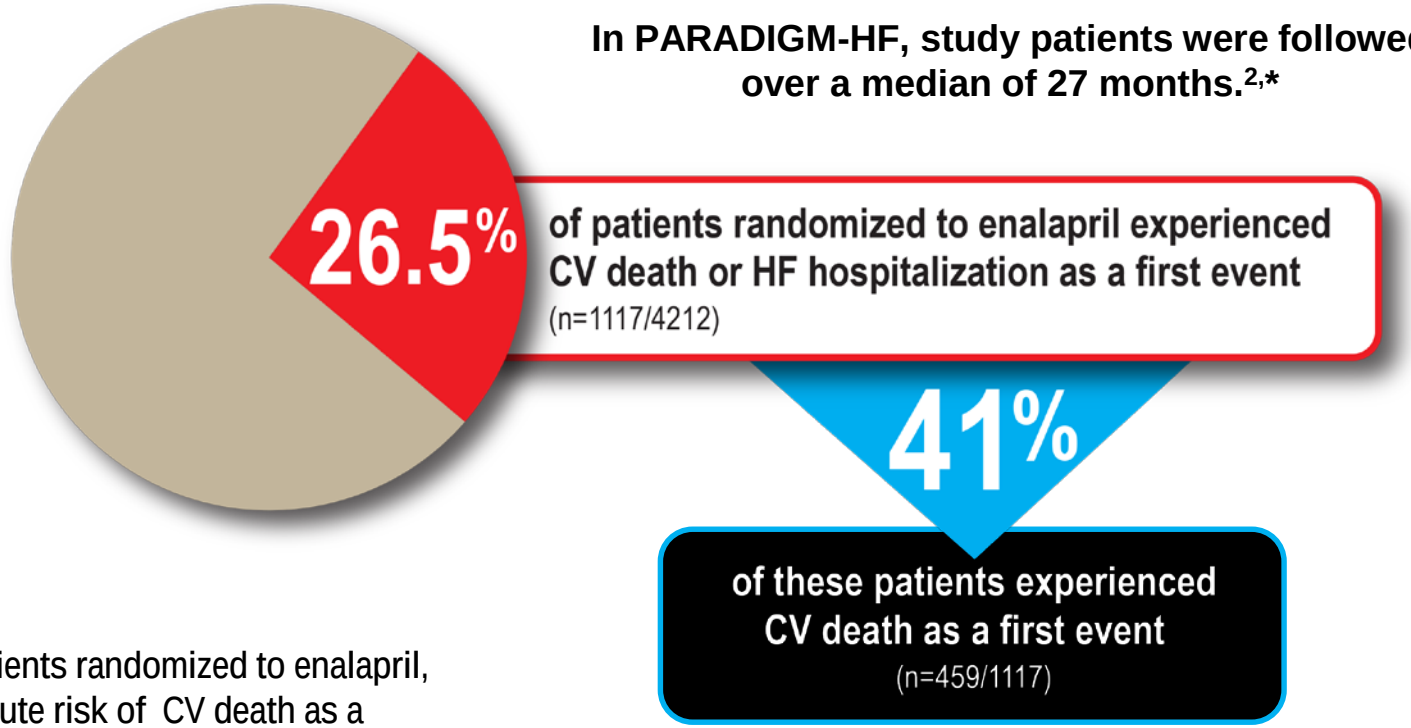
Yancy CW, et al. *J Am Coll Cardiol*. 2013;62:1495-1539.

Pharmacologic Treatment for Stage C HFrEF



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

Residual Risk for HFrEF Despite Conventional GDMT

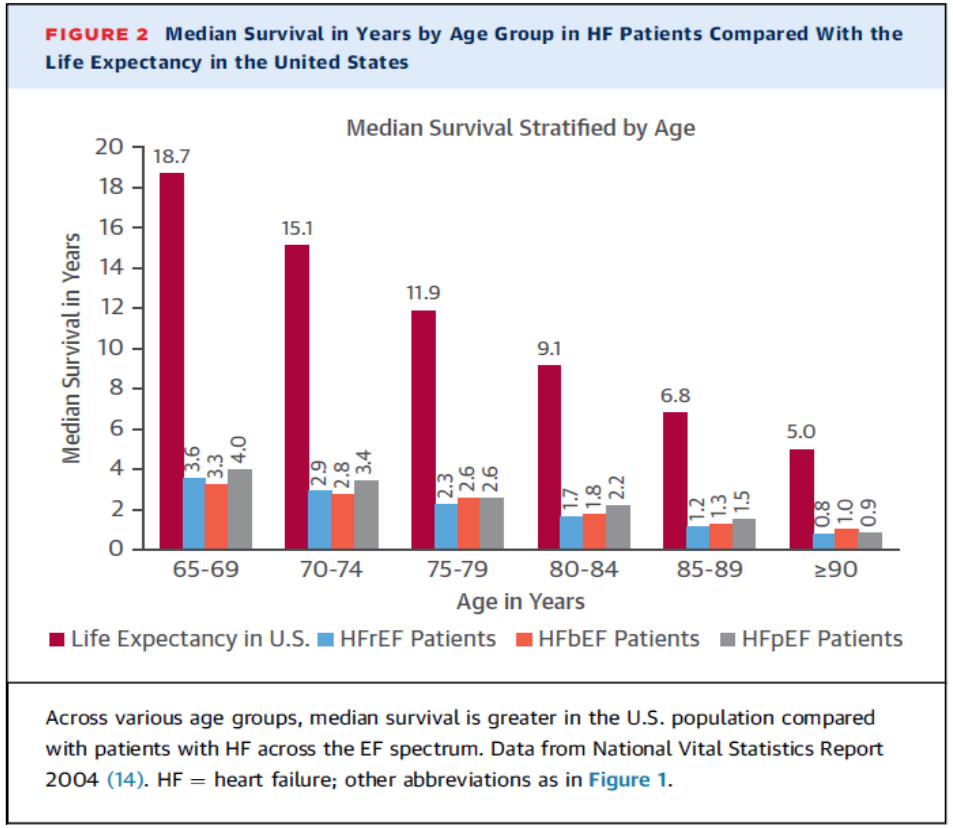


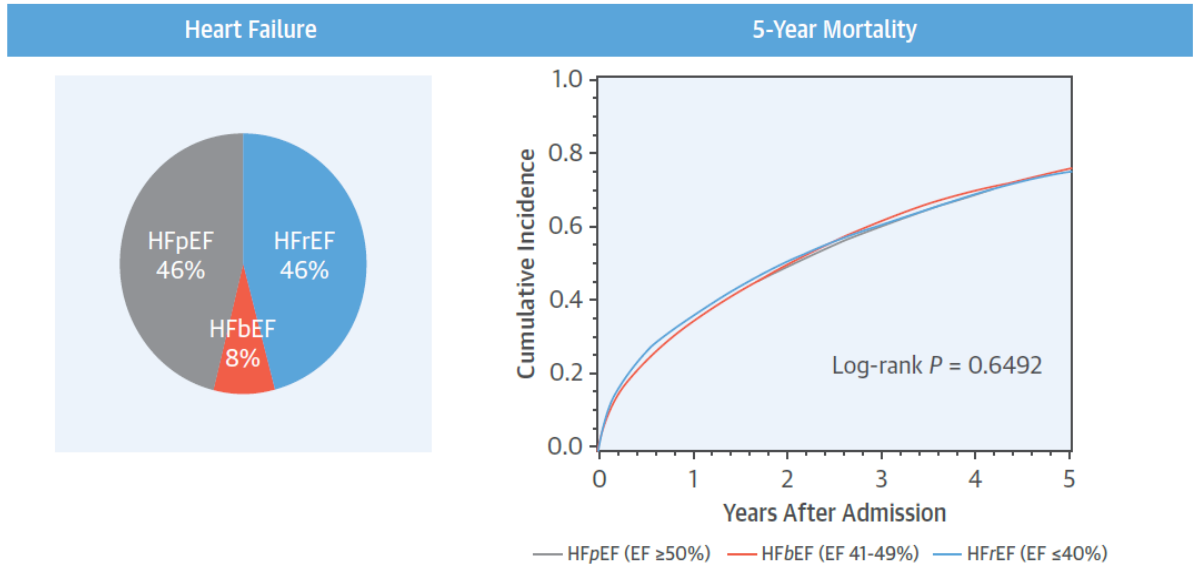
Of all patients randomized to enalapril, the absolute risk of CV death as a first event was 10.9% (n=459/4212)[1]

*Adult patients with NYHA class II–IV symptoms and an ejection fraction of 40% or less were required to take a stable dose of a beta blocker and an ACE inhibitor (or ARB) equivalent to at least 10 mg of enalapril daily, with most also receiving MRA.

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

5 Year Outcomes for Heart Failure



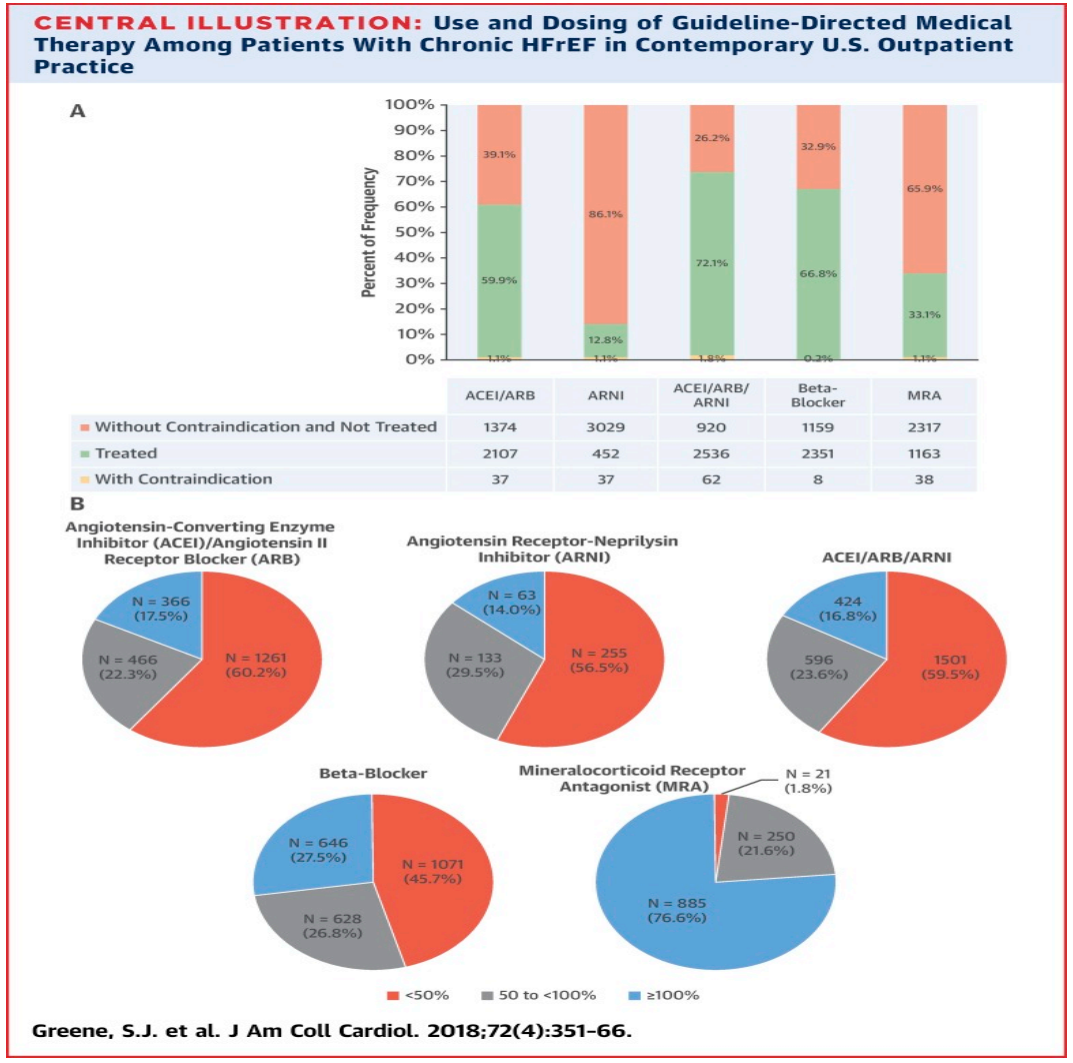


Outcomes – 5-Year Event Rates (%)					
	Mortality	Readmission	CV Readmission	HF Readmission	Mortality/Readmission
HFrEF	75.3	82.2	63.9	48.5	96.4
HFbEF	75.7	85.7	63.3	45.2	97.2
HFpEF	75.7	84.0	58.9	40.5	97.3

Long-term prognosis with hospitalization with HF is poor, irrespective of EF

Shah K, et al J Am Coll Cardiol 2017;70:2476–86

Use and Dosing of GDMT for HFrEF: Outpatient CHAMP HF Registry



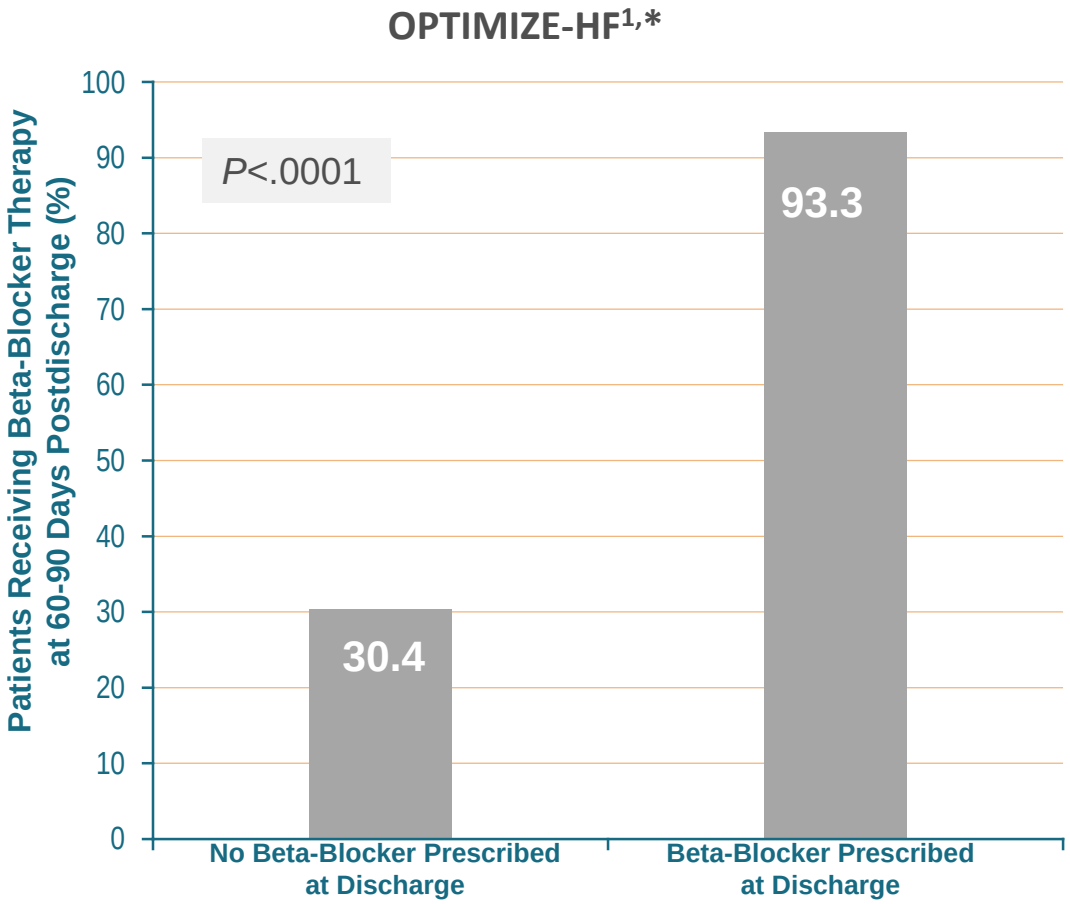
3,518 HFrEF patients without contraindications or intolerance to GDMT from 150 primary care and cardiology practices 2016-2018

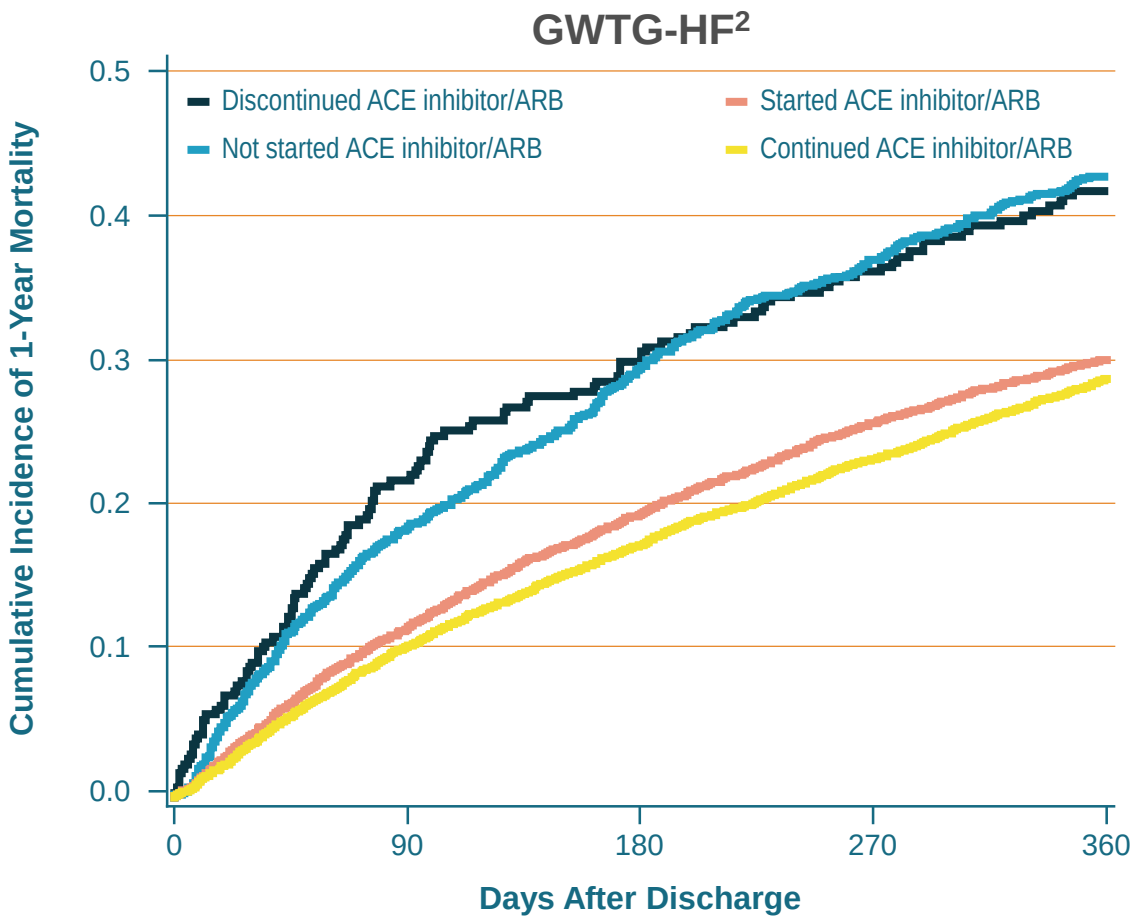
When medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%), whereas most patients were receiving target doses of MRA therapy (77%).

Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA.

Greene S, Fonarow GC et al JACC 2019,72:351.-6.

Patients Leaving the Hospital on GDMT Have Improved Treatment Adherence and Outcomes





*Initiation of a beta-blocker did not affect length of stay (LoS).[1]

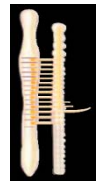
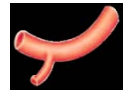
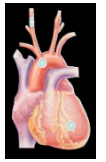
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GDMT, guideline-directed medical therapy; GWTG-HF, Get With The Guidelines®-Heart Failure; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure.

1. Fonarow GC, et al. *Am Heart J.* 2007;153(1):82.e1-82.e11. 2. Gilstrap LG, et al. *J Am Heart Assoc.* 2017;6(2):e004675.

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

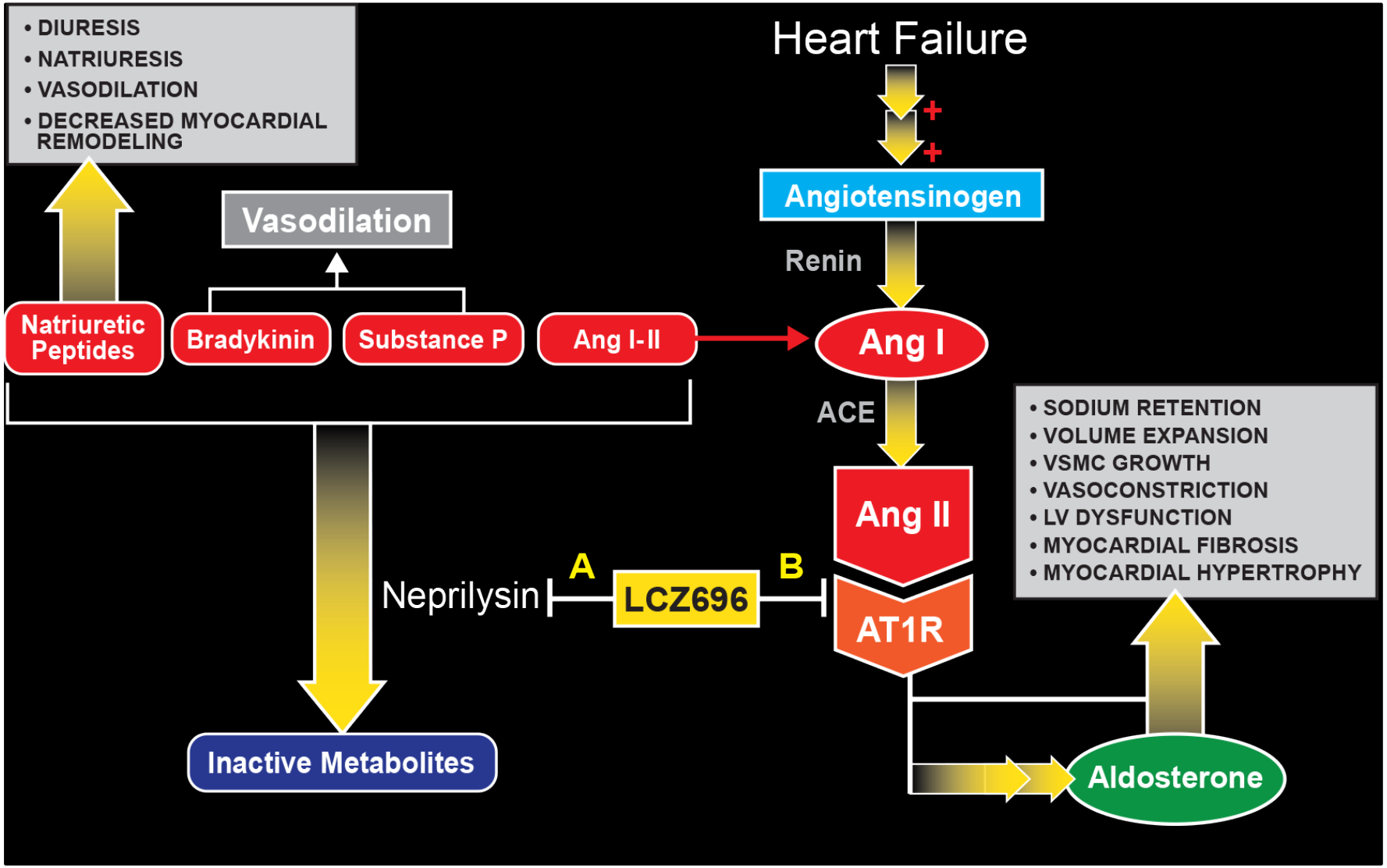
Neprilysin inhibition

Inactive metabolites

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

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)

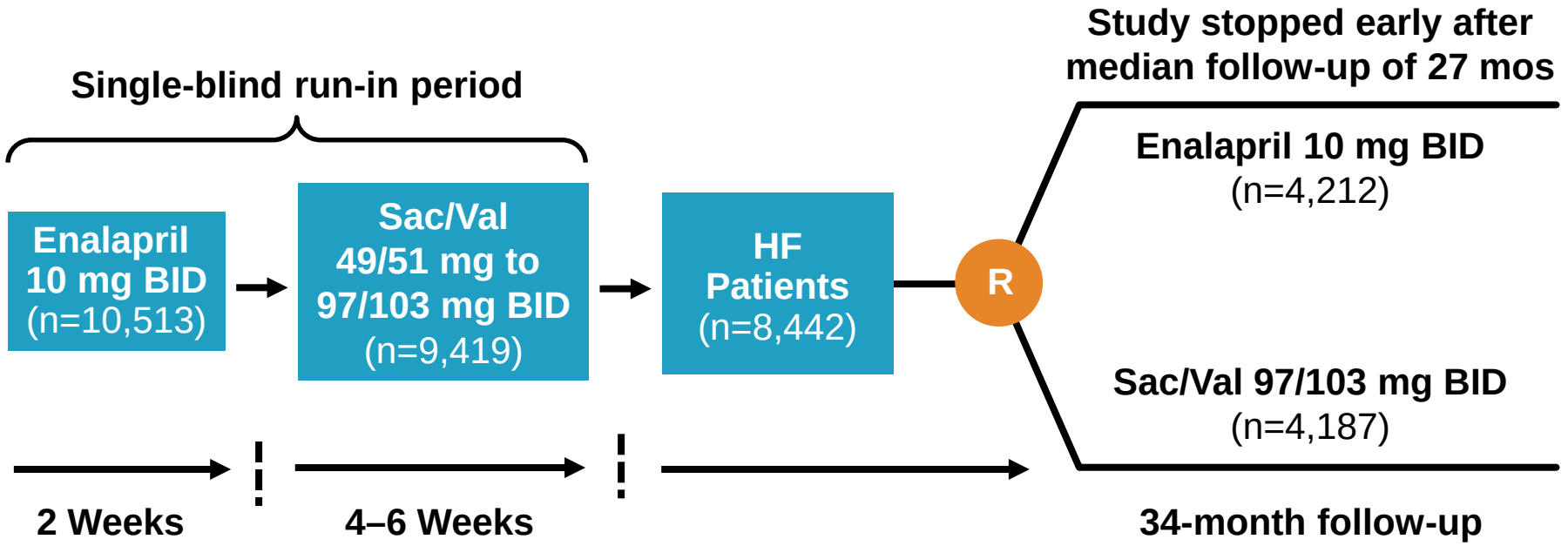
Sacubitril/Valsartan 97/103 mg twice daily ⟷ **Enalapril 10 mg twice daily**

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

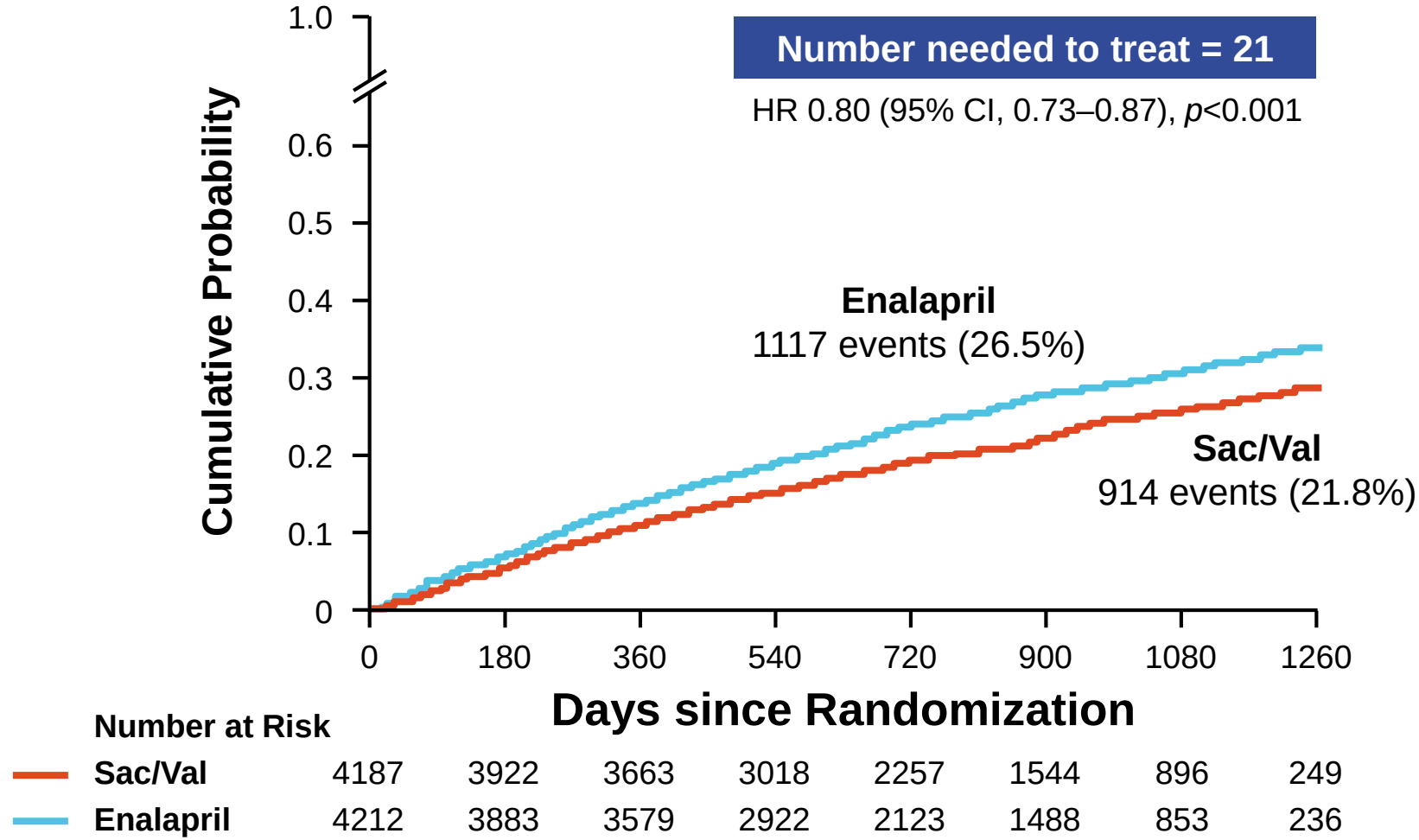


Primary endpoint: Death from CV causes or hospitalization for HF

Sac/Val = Sacubitril/Valsartan.

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

PARADIGM-HF: 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.

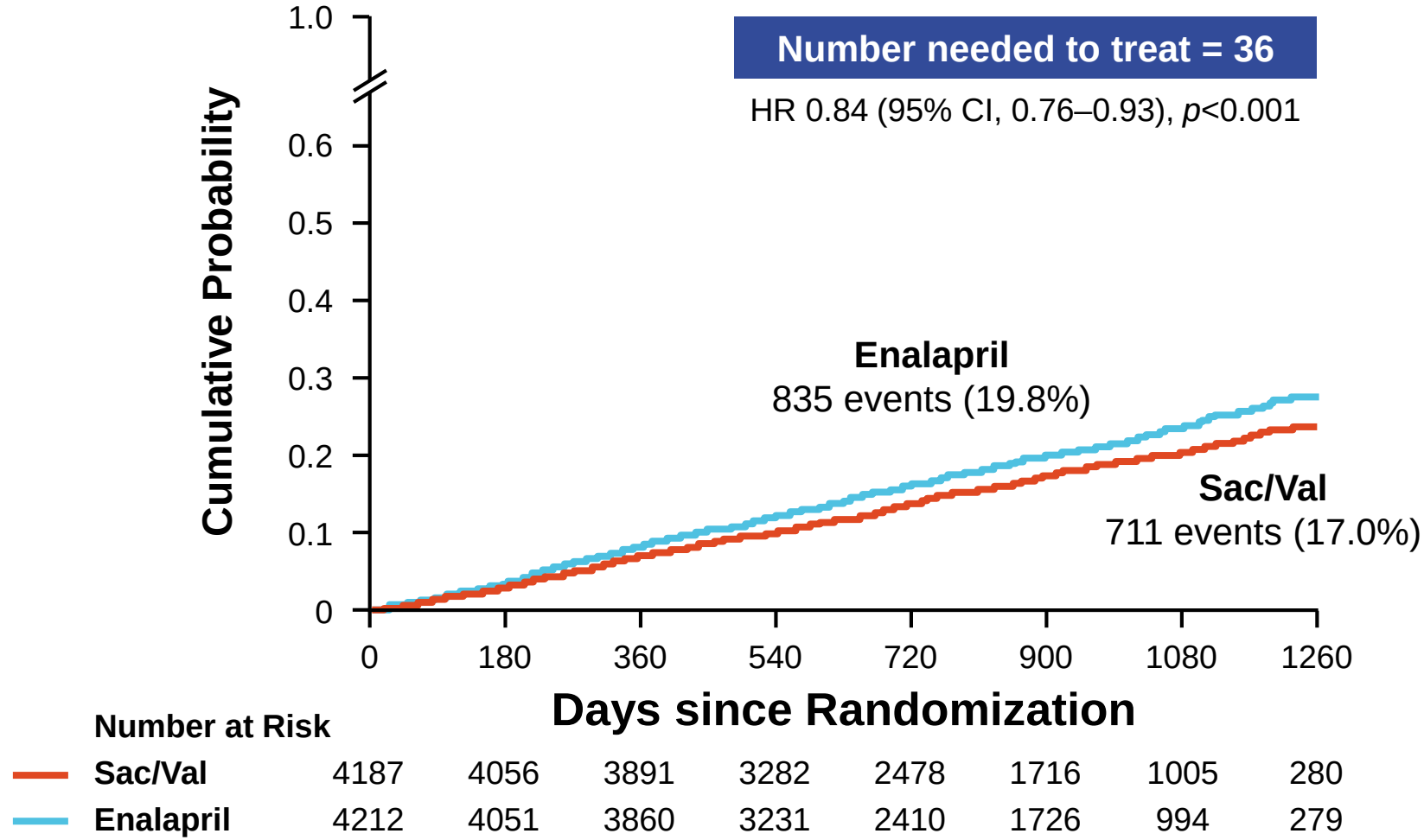
PARADIGM-HF: Effect of Sac/Val vs. Enalapril on the Primary Endpoint and Its Components

	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.

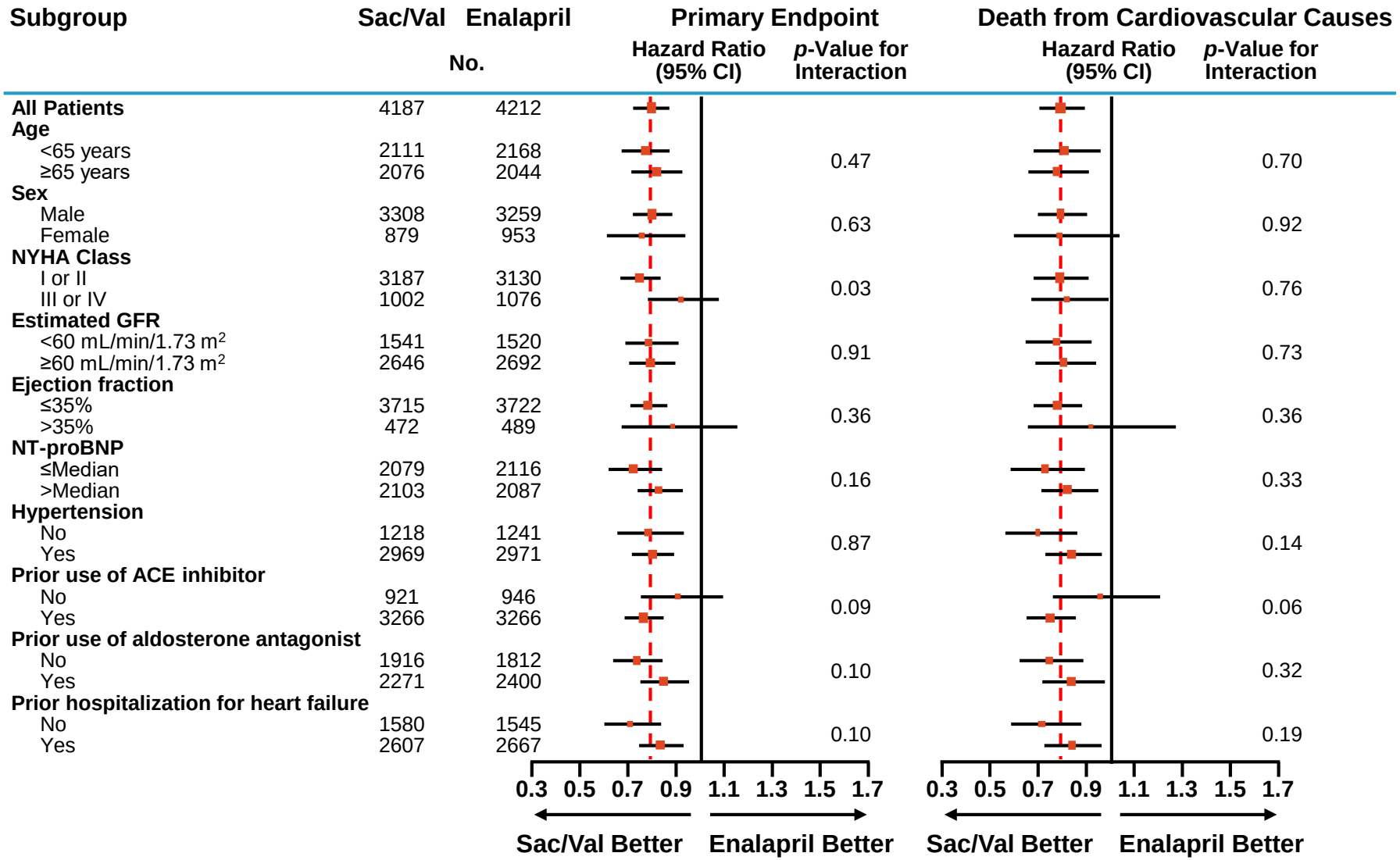
PARADIGM-HF: All-Cause Mortality



Sac/Val = Sacubitril/Valsartan.

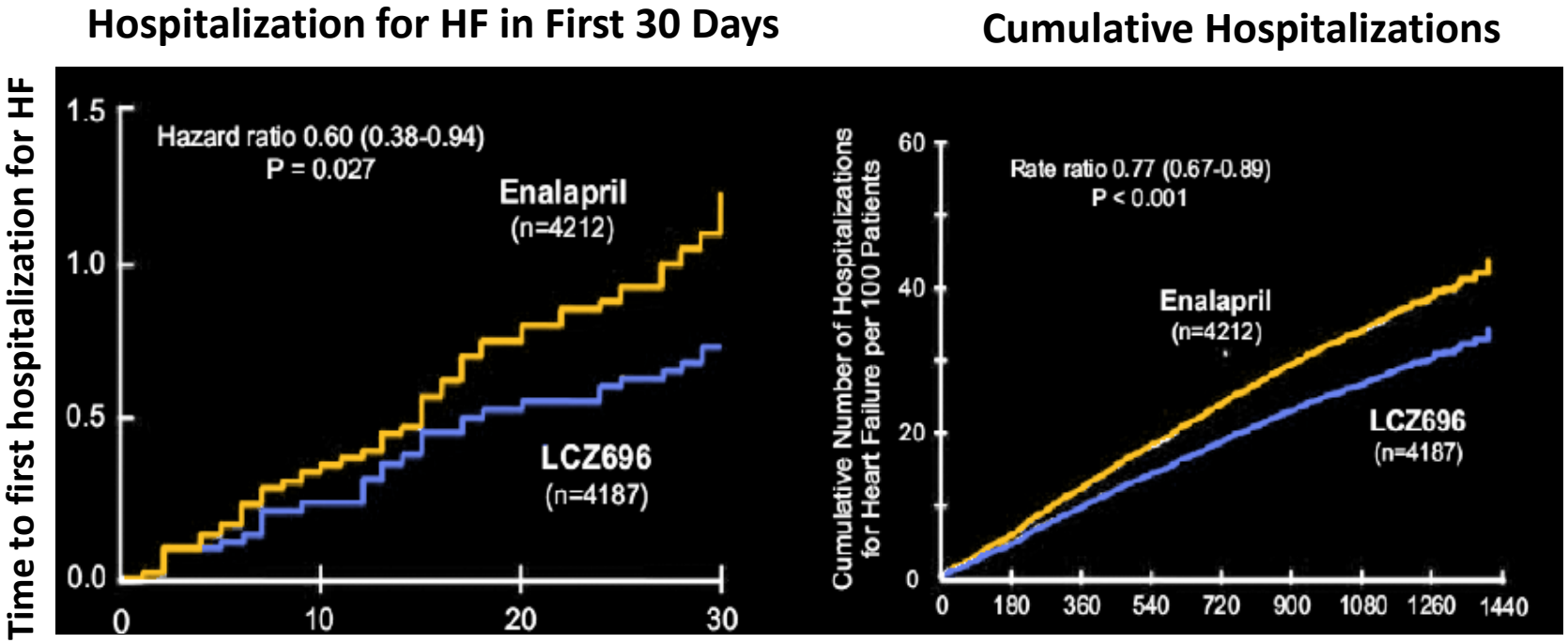
McMurray JJV, et al. *N Engl J Med.* 2014;371:993-1004.

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.

Effect of Sacubitril/Valsartan on Early and Late Measures of HF Progression



Patients at Risk

LCZ696	4187	4174	4153	4140	4187	4054	3885	3276	2472	1710	1001	279	12
Enalapril	4212	4192	4166	4143	4212	4049	3857	3228	2408	1724	993	278	17

Packer M et al. *Circulation.* 2015;131:54-61.

2016 ACC/AHA/HFSA Heart Failure Guideline Update

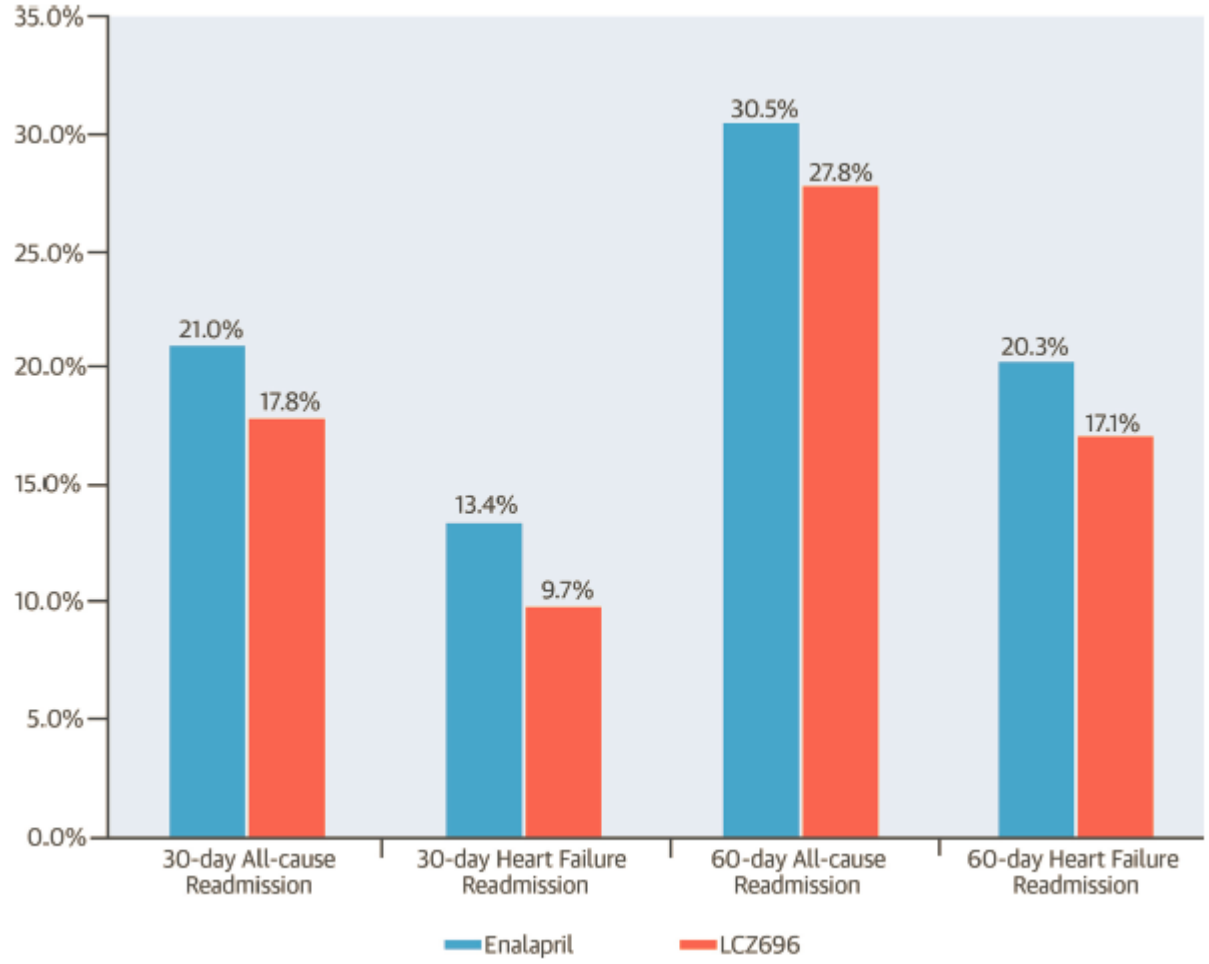
Pharmacological Treatment for Stage C HF*r*EF

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI		
COR	**LOE**	**Recommendations**
I	ACE: A ARB: A ARNI: B-R	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.
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].

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

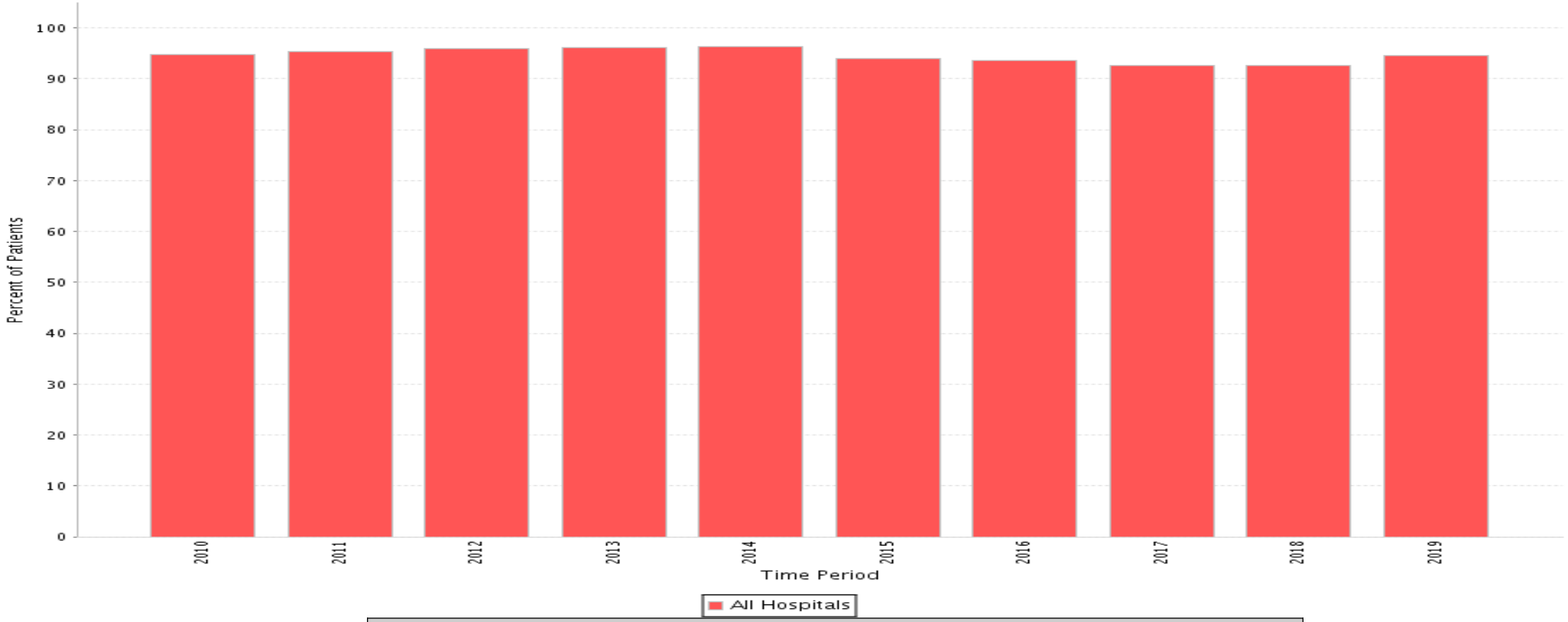
2,383 investigator-reported HF hospitalizations, of which 1,076 (45.2%) occurred in subjects assigned to sacubitril/valsartan and 1,307 (54.8%) occurred in subjects assigned to enalapril.

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

GWTG-HF Data on ACEI/ARB or ARNI at Discharge*

Percent of heart failure patients with left ventricular systolic dysfunction (LVSD) and without angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) or angiotensin-receptor/neprilysin inhibitor (ARNI) contraindications who are prescribed an ACEI, ARB, or ARNI at hospital discharge.

Time Period: 01/2010 - 01/2019

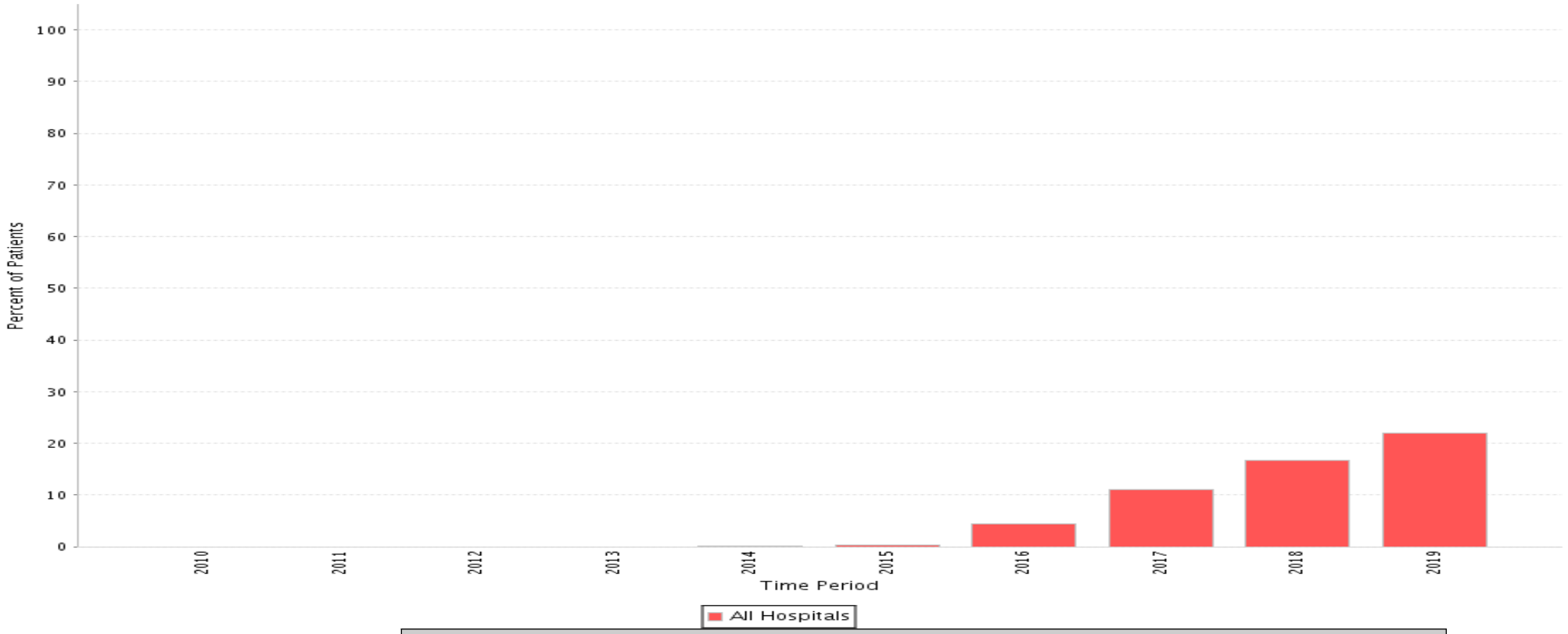


Data For: ACEI/ARB or ARNI at Discharge*				
Benchmark Group	Time Period	Numerator	Denominator	% of Patients
All Hospitals	2010	35947	37974	94.7%
All Hospitals	2011	36960	38791	95.3%
All Hospitals	2012	35702	37215	95.9%
All Hospitals	2013	35615	37036	96.2%
All Hospitals	2014	35677	37029	96.3%
All Hospitals	2015	36394	38728	94.0%
All Hospitals	2016	37913	40498	93.6%
All Hospitals	2017	38446	41558	92.5%
All Hospitals	2018	34270	37015	92.6%
All Hospitals	2019	481	509	94.5%

American Heart Association.

GWTG-HF Data Angiotensin Receptor-Neprilysin Inhibitor (ARNI) at Discharge

Percentage of eligible patients with heart failure who are prescribed an ARNI at hospital discharge.
Time Period: 01/2010 - 01/2019



Data For: Angiotensin Receptor-Neprilysin Inhibitor (ARNI) at Discharge				
Benchmark Group	Time Period	Numerator	Denominator	% of Patients
All Hospitals	2010	0	35939	0.0%
All Hospitals	2011	0	37078	0.0%
All Hospitals	2012	0	35636	0.0%
All Hospitals	2013	0	35487	0.0%
All Hospitals	2014	1	35046	0.0%
All Hospitals	2015	83	34393	0.2%
All Hospitals	2016	1456	32811	4.4%
All Hospitals	2017	3302	30090	11.0%
All Hospitals	2018	4402	26416	16.7%
All Hospitals	2019	82	373	22.0%

American Heart Association.

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

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

[1]Yale Univ Sch of Med, New Haven, CT; [2]Harvard Univ/Brigham and Women's Hosp, Boston, MA; [3]Duke Univ/Duke Clinical Res Inst, Durham, NC; [4]Novartis Pharmaceuticals Corp, East Hanover, NJ; [5]

Background

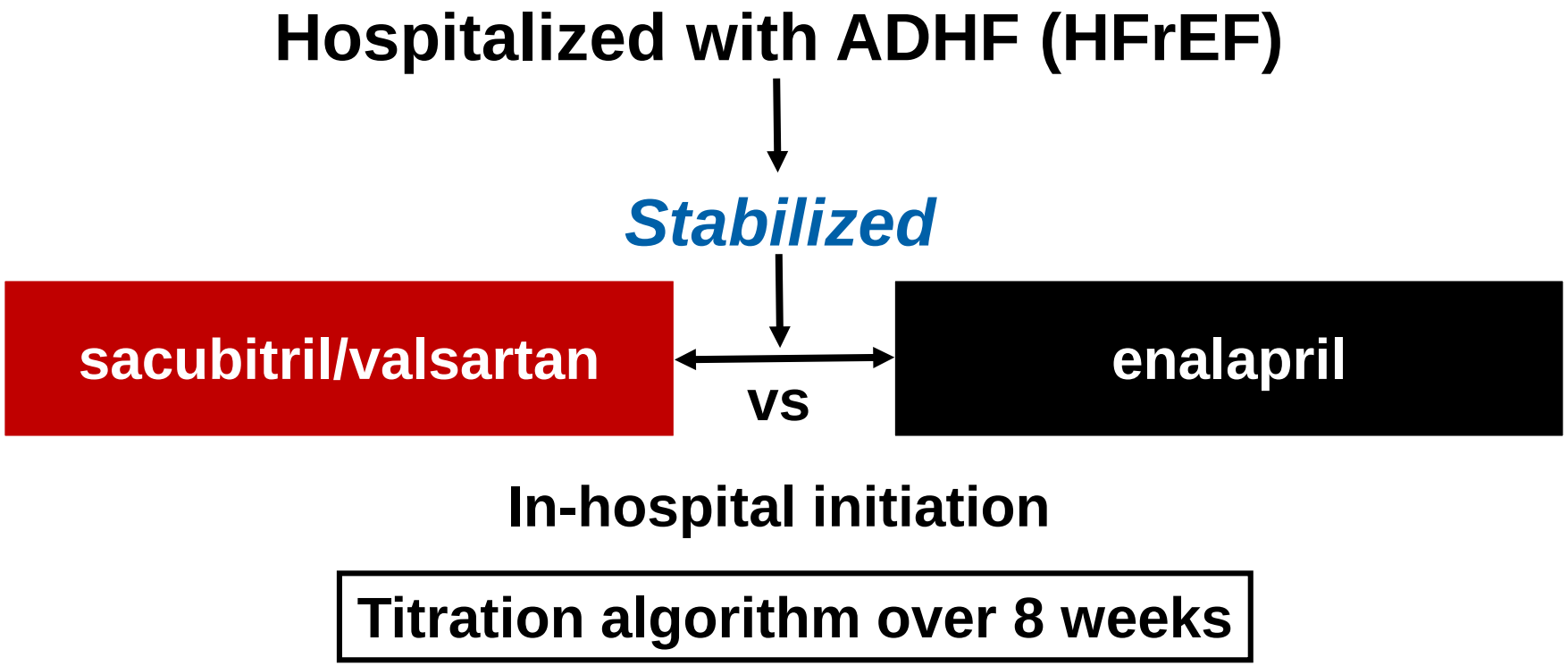
- **Acute decompensated heart failure (ADHF) accounts for over 1M hospitalizations in the US annually**
- **Guideline-directed therapy for ADHF is limited**
  - **Decongestion with diuretics and hemodynamic support with vasodilators remain the standards of care**

Rationale

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

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

Study Design



In-hospital initiation

Titration algorithm over 8 weeks

- **Evaluate biomarker surrogates of efficacy**
- **Evaluate safety and tolerability**
- **Explore clinical outcomes**

Key Entry Criteria

- Hospitalized for ADHF (signs and symptoms of fluid overload)
- LVEF ≤40% within the last 6 months
- NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL (screening)
- Stabilized while still hospitalized
  - In the prior 6 hours:
    - SBP ≥100 mmHg, no symptomatic hypotension
    - No increase in IV diuretics
    - No IV vasodilators
  - In the prior 24 hours: no IV inotropes

Key Endpoints

- **Primary endpoint:** **Proportional change in NT-proBNP from baseline to the mean of weeks 4 and 8**
- **Safety**
  - **Worsening renal function**
  - **Hyperkalemia**
  - **Symptomatic hypotension**
  - **Angioedema**
- **Exploratory Clinical Outcomes**
  - **Serious clinical composite: death, re-hospitalization for HF, LVAD, or listing for cardiac transplant**
  - **Expanded composite: Serious composite + addition of HF med, unplanned outpatient IV diuretics or >50% increase in dose**

SBP Dose Titration Algorithm

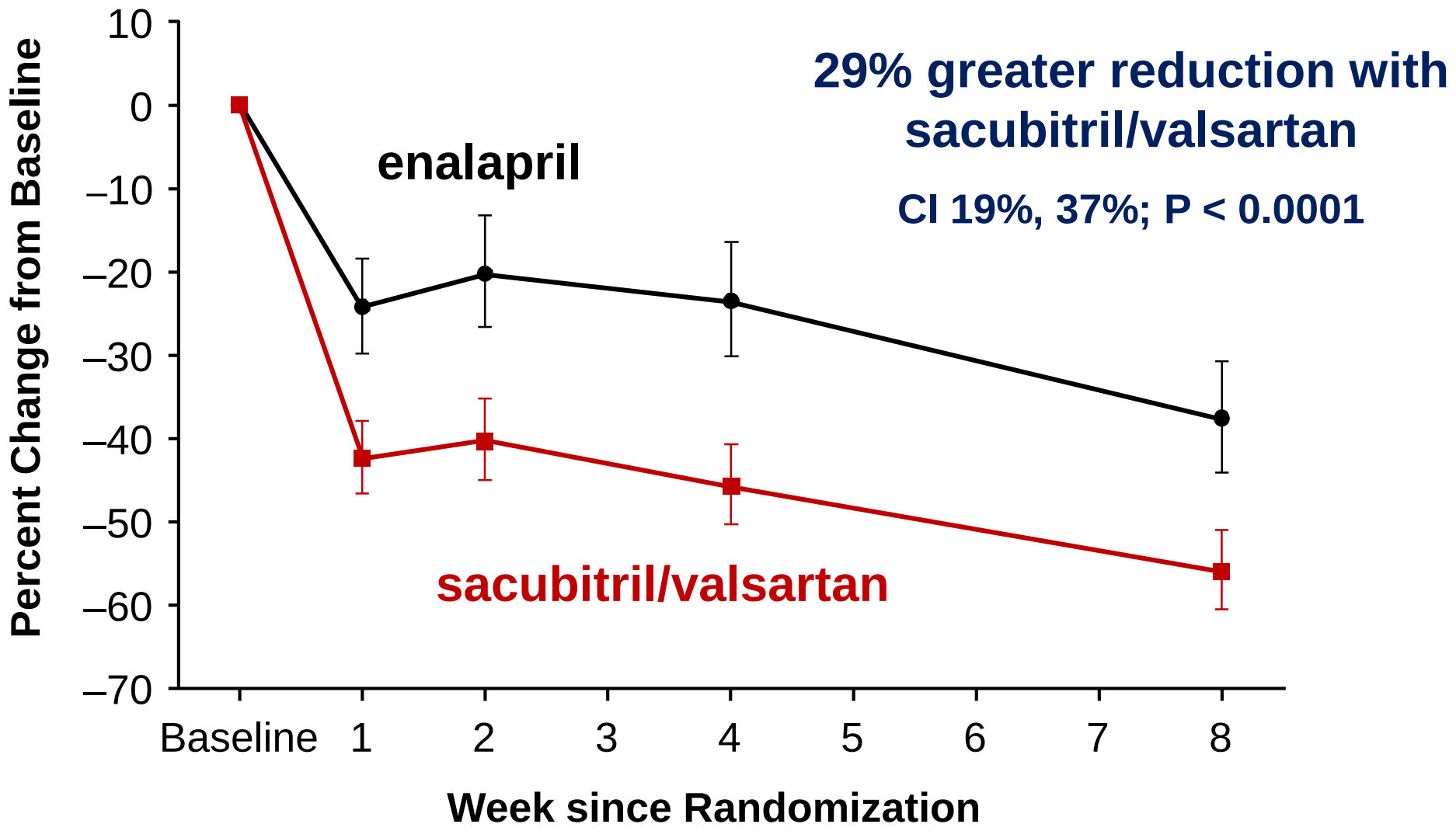
- **Starting dose level based on SBP**
  - **If 100 to <120 mm Hg, sacubitril/valsartan 24/26 mg or enalapril 2.5 mg twice daily**
  - **If ≥120 mm Hg, sacubitril/valsartan 49/51 mg or enalapril 5 mg twice daily**
- **Up-titration based on SBP (clinical judgement permitted)**
- **Target doses**
  - **sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily**

Baseline Characteristics

	sacubitril/valsartan (n=440)	enalapril (n=441)
Age* (years)	61 (51, 71)	63 (54, 72)
Women (%)	25.7	30.2
Black (%)	35.9	35.8
No prior HF diagnosis (%)	32.3	37.0
No ACEi/ARB therapy (%)	52.7	51.5
LVEF*	0.24 (0.18, 0.30)	0.25 (0.20, 0.30)
SBP (mm Hg)*	118 (110, 133)	118 (109, 132)
NT-proBNP (pg/mL)*	2883 (1610, 5403)	2536 (1363, 4917)

*Median (interquartile range) .

Primary Endpoint: % Change in NT-proBNP



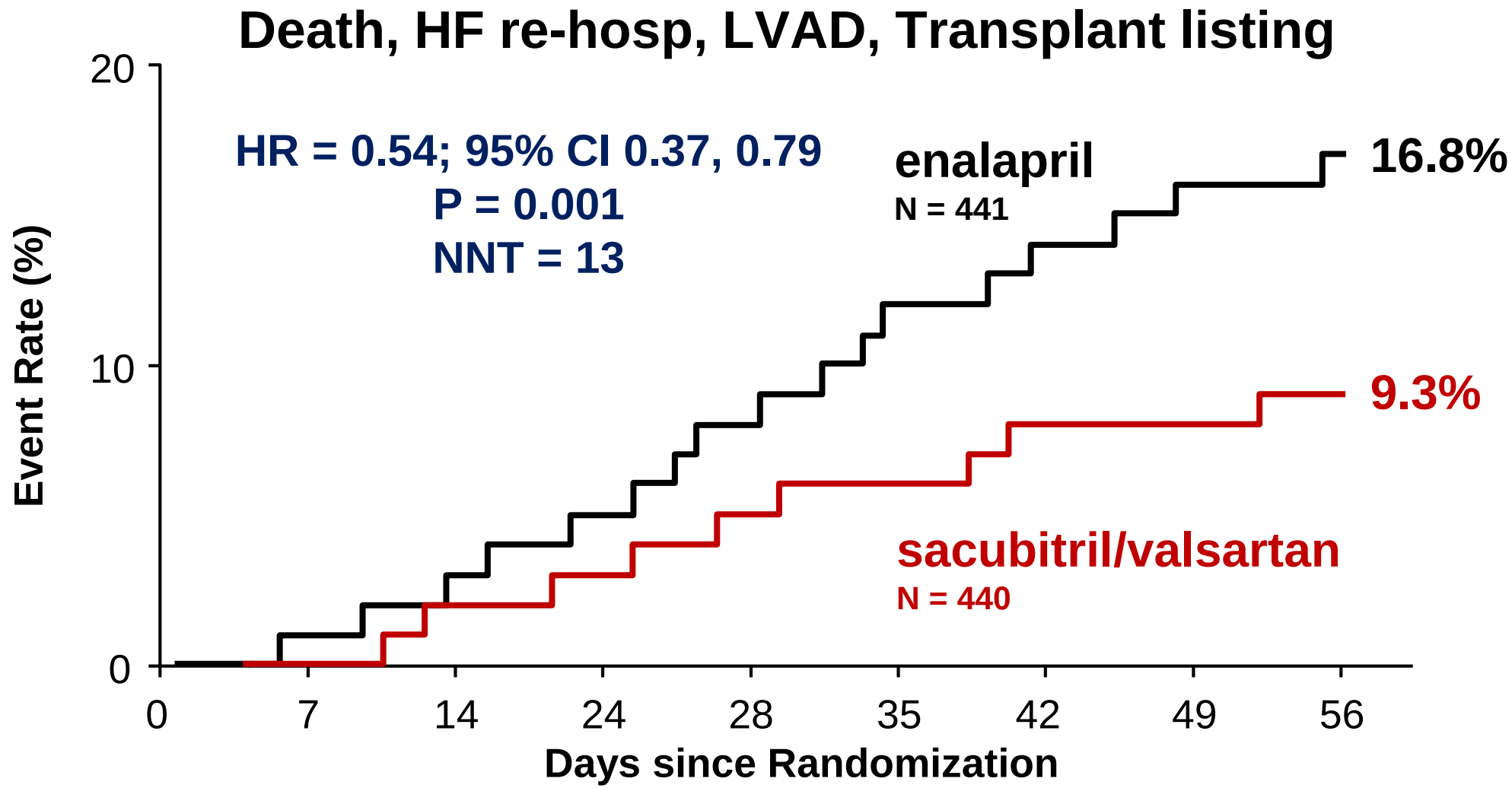
Safety

Safety Events (%)	sacubitril/ valsartan (n=440)	enalapril (n=441)	RR (95% CI)
Worsening renal function*	13.6	14.7	0.93 (0.67-1.28)
Hyperkalemia†	11.6	9.3	1.25 (0.84-1.84)
Symptomatic hypotension	15.0	12.7	1.18 (0.85-1.64)
Angioedema event	1 (0.2%)	6 (1.4%)	0.17 (0.02-1.38)

P = NS for all safety events

*Cr ≥0.5 with simultaneous reduction in eGFR of ≥25%
†K+ >5.5 mg/dl

Serious Composite Clinical Endpoint

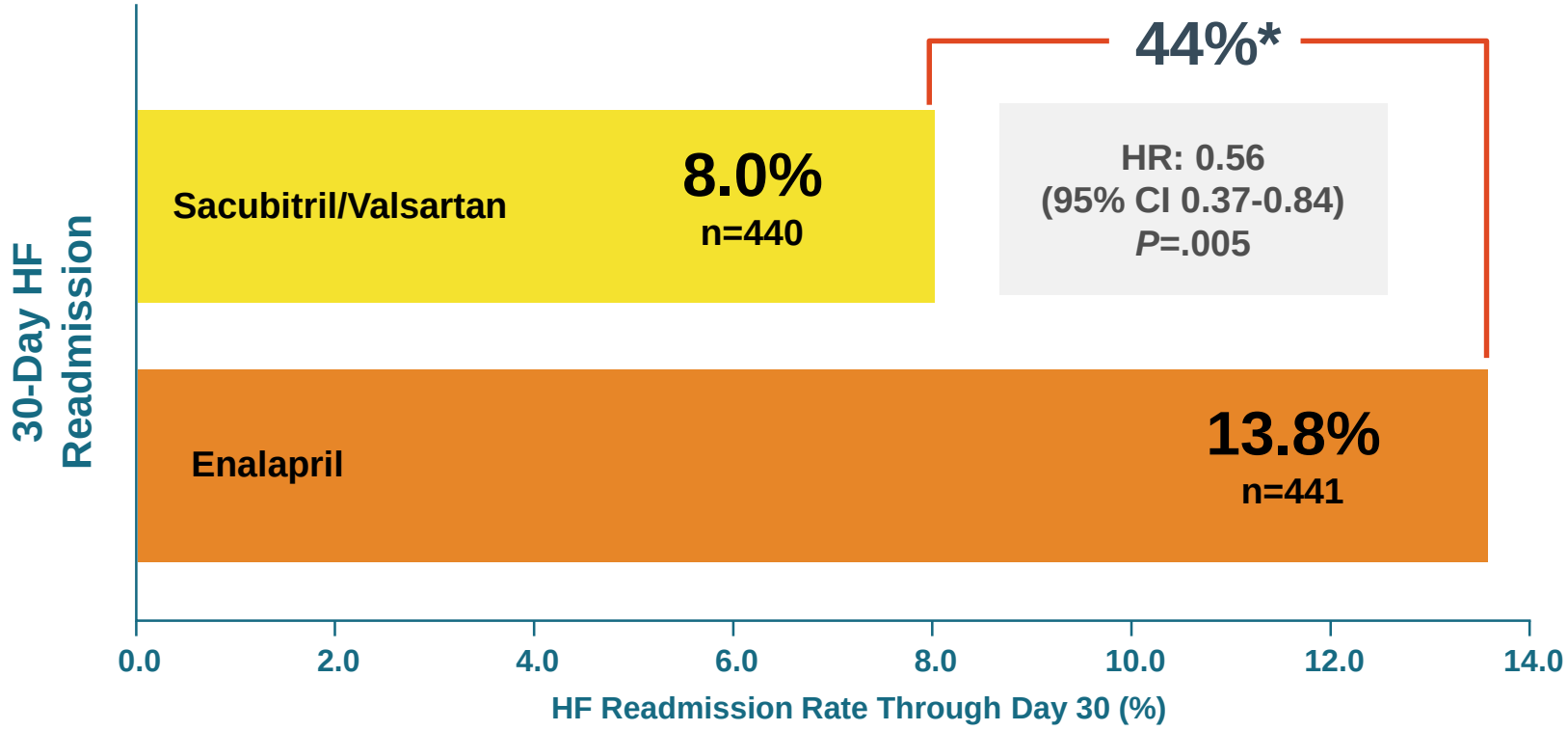


Exploratory Clinical Endpoints

	sacubitril/ valsartan (n=440)	enalapril (n=441)	HR	P-value
Serious Composite, %	**9.3**	**16.8**	**0.54**	**0.001**
Death, %	2.3	3.4	0.66	0.311
Re-hosp for HF, %	8.0	13.8	0.56	0.005
LVAD, %	0.2	0.2	0.99	0.999
Cardiac Transplant, %	0	0	-	-
Expanded Composite*, %	**56.6**	**59.9**	**0.93**	**0.369**
Unplanned IV diuretics, %	0.5	0.5	0.99	0.997
Addition of HF med, %	17.7	19.1	0.92	0.58
>50% diuretic increase, %	49.6	50.3	0.98	0.812

*Serious composite + addition of HF med, no unplanned outpatient IV diuretics or >50% increase in dose

PIONEER-HF: Exploratory Clinical Outcomes
30-Day HF Readmission

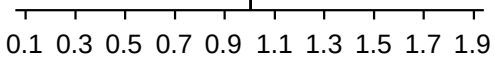


5.8% Absolute Risk Reduction

Key Subgroup Analyses

Change in NT-proBNP

Subgroup	sacubitril/valsartan vs. enalapril mean [95% CI]
All Patients	0.71 [0.63, 0.81]
Prior HF	
No	0.65 [0.53, 0.81]
Yes	0.72 [0.63, 0.83]
Prior ACEi/ARB	
No	0.72 [0.60, 0.86]
Yes	0.72 [0.61, 0.85]

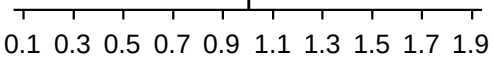


Favors sacubitril / valsartan

Favors enalapril

Serious Composite Endpoint

Subgroup	Hazard Ratio [95% CI]
All Patients	0.54 [0.37, 0.79]
Prior HF	
No	0.37 [0.12, 1.15]
Yes	0.53 [0.35, 0.80]
Prior ACEi/ARB	
No	0.52 [0.29, 0.95]
Yes	0.56 [0.34, 0.92]



Favors sacubitril / valsartan

Favors enalapril

P value (interaction) = NS

Conclusions

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

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

Clinical Implications

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

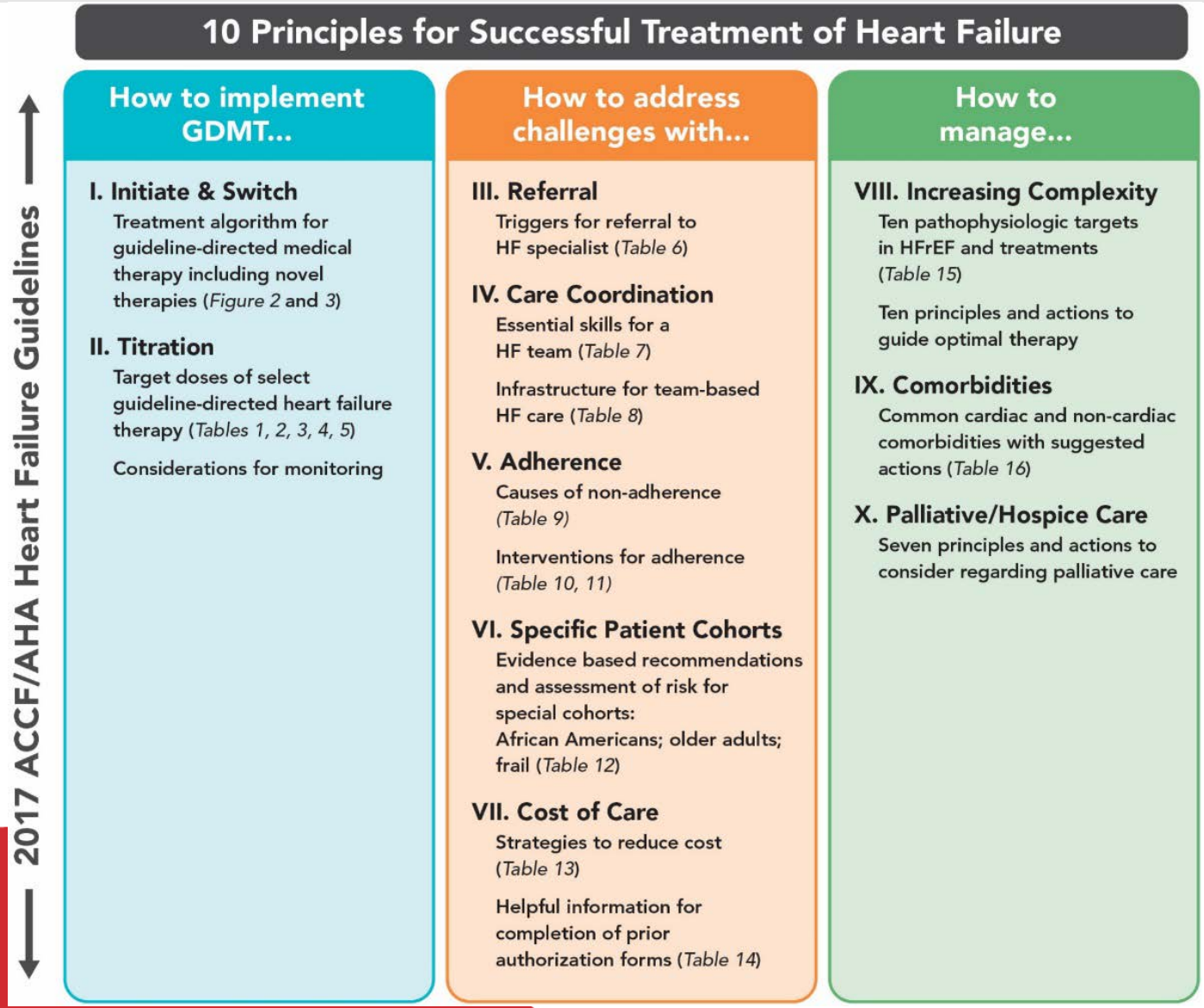
Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

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

Practical Points on Use of Sacubitril/Valsartan

- Starting dose is 24/26 mg twice daily, unless patient is 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, aim for target dose
- In-hospital initiation is safe, well tolerated, and improves early outcomes
- 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

2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment



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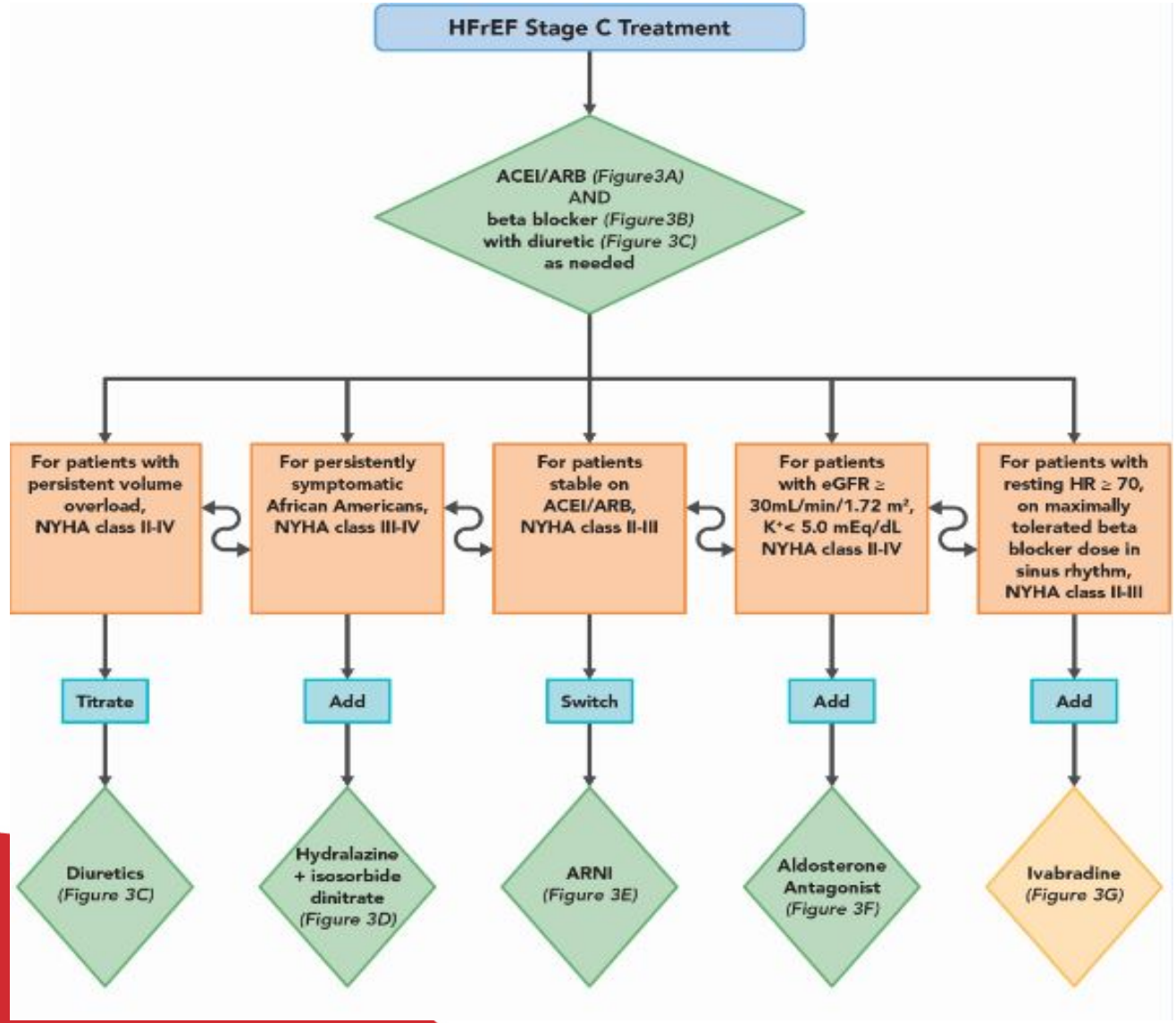
Treatment Algorithm for Guideline-Directed Medical Therapy Including Novel Therapies



Excerpted from:

Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection Fraction

December 2017
DOI: 10.1016/j.jacc.2017.11.025

AMERICAN COLLEGE of CARDIOLOGY

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EVIDENCE-BASED HFREF THERAPIES

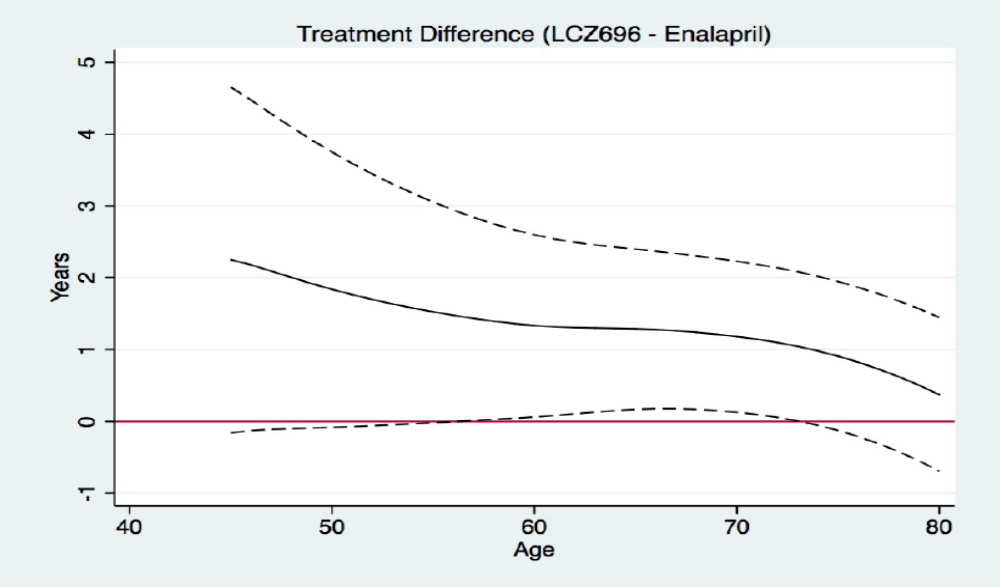
Guideline Recommended Therapy	Relative Risk Reduction in Mortality	Number Needed to Treat for Mortality	NNT for Mortality (standardized to 36 months)	Relative Risk Reduction in HF Hospitalizations
ACEI/ARB	17%	22 over 42 months	26	31%
ARNI	16%	36 over 27 months	27	21%
Beta-blocker	34%	28 over 12 months	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.

Cost-Effectiveness and Value of Sacubitril/Valsartan Replacing Enalapril in HFrEF[1]

- For every 100 000 people receiving sacubitril/valsartan, this strategy could potentially reduce hospitalizations by 3000 and reduce deaths by nearly the same number over a 2-year period. Medical savings from reduced HF admissions would be more than $27 million.

What Value Do You and Your Patients Place on Being Able to Live 1-2 Years on Average Longer?



1. Gaziano TA et al. *JAMA Cardiol. 2016;16:666-672.*

N Engl J Med 2015;373;23

Potential Mortality Reduction With Implementation of Sacubitril/Valsartan Therapy

Potential Benefit

5,700,000 patients with HF in the United States

→ 2,964,000 excluded with HFpEF

2,736,000 HFrEF

→ 136,800 excluded
•109,440 in hospice or comfort care only
•27,360 receiving advanced therapies

2,599,200 HFrEF

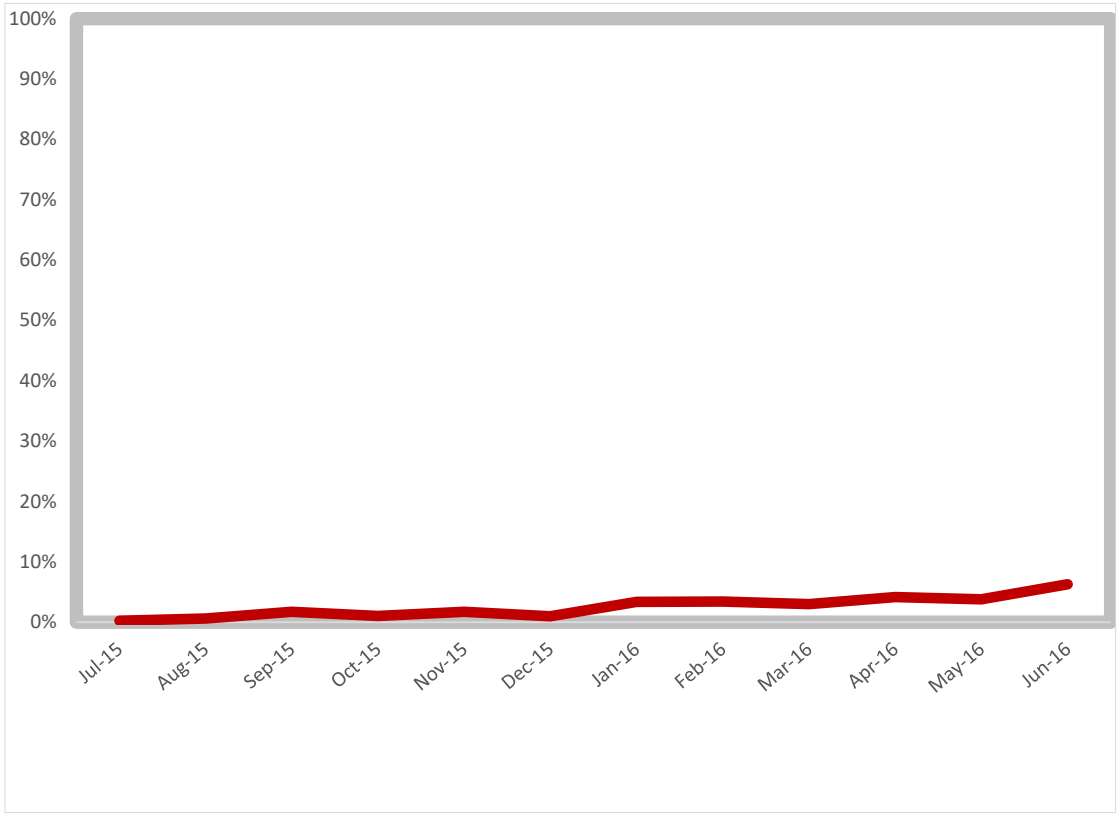
→ 311,904 excluded
•181,944 with contraindication for or intolerance to ACE inhibitor/ARB/ARNI
•129,960 with SBP <95 mm Hg

2,287,296 HFrEF eligible for ARNI

Optimal implementation of ARNI therapy was empirically estimated to prevent 28,484 (range, 18,230-41,017) deaths per year

Fonarow GC, et al. *JAMA Cardiol.* 2016. doi:10.1001/jamacardio.2016.1724.

Actual Practice



ARNI Use in Eligible HFrEF Patients

J Am Coll Cardiol HF 2017;5:305-9.

Hospital Level Variation in the Early Adoption of ARNI in HFrEF

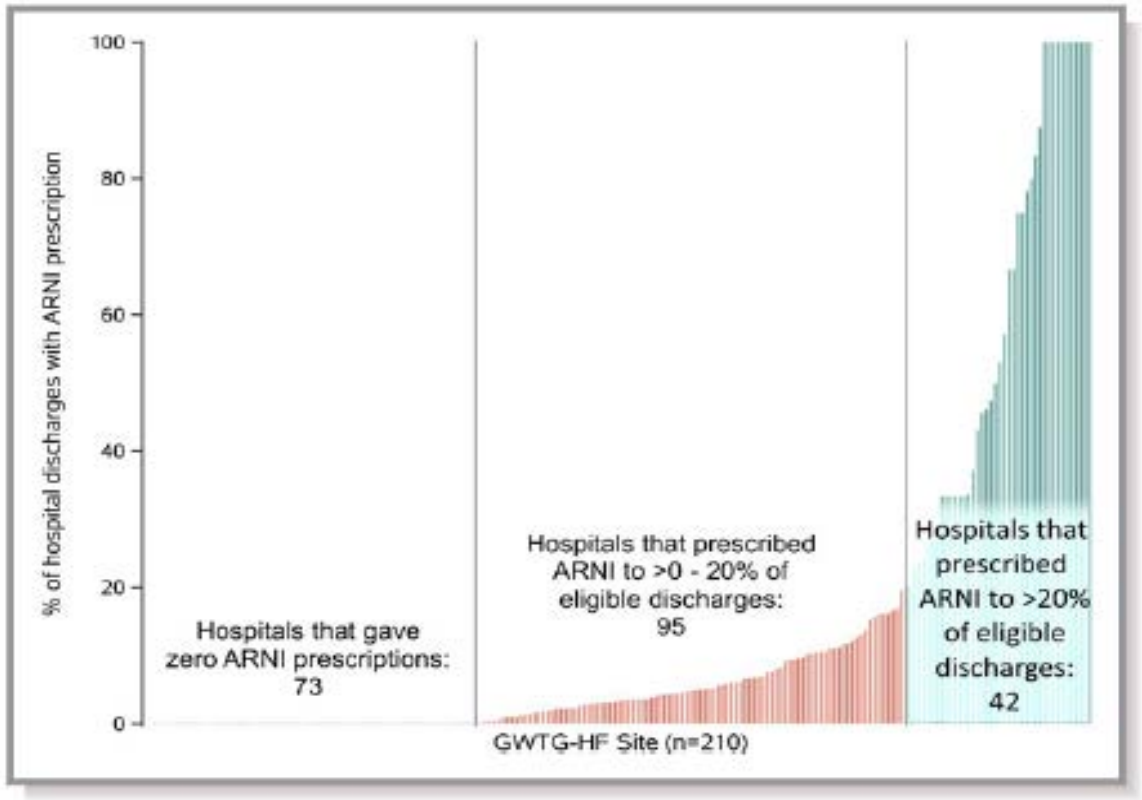
Relationship Between Hospital Characteristics and Early Adoption of Angiotensin-Receptor/Neprilysin Inhibitor Among Eligible Patients Hospitalized for Heart Failure

Nancy Luo, MD; Steven J. Lippmann, PhD; Robert J. Mentz, MD; Melissa A. Greiner, MS; Bradley G. Hammill, DrPH; N. Chantelle Hardy, MPH; Warren K. Laskey, MD, MPH; Paul A. Heidenreich, MD, MS; Chun-Lan Chang, PhD; Adrian F. Hernandez, MD, MHS; Lesley H. Curtis, PhD; Pamela N. Peterson, MD, MSPH; Gregg C. Fonarow, MD; Emily C. O'Brien, PhD

Background—The angiotensin-receptor/neprilysin inhibitor (ARNI) sacubitril/valsartan reduces hospitalization and mortality for patients with heart failure with reduced ejection fraction. However, adoption of ARNI into clinical practice has been slow. Factors influencing use of ARNI have not been fully elucidated. Using data from the Get With The Guidelines-Heart Failure registry, Hospital Compare, Dartmouth Atlas, and the American Hospital Association Survey, we sought to identify hospital characteristics associated with patient-level receipt of an ARNI prescription.

Methods and Results—We analyzed patients with heart failure with reduced ejection fraction who were eligible for ARNI prescription (ejection fraction≤40%, no contraindications) and hospitalized from October 1, 2015 through December 31, 2016. We used logistic regression to estimate the associations between hospital characteristics and patient ARNI prescription at hospital discharge, accounting for clustering of patients within hospitals using generalized estimating equation methods and adjusting for patient-level covariates. Of 16 674 eligible hospitalizations from 210 hospitals, 1020 patients (6.1%) were prescribed ARNI at discharge. The median hospital-level proportion of patients prescribed ARNI was 3.3% (Q1, Q3: 0%, 12.6%). After adjustment for patient-level covariates, for-profit hospitals had significantly higher odds of ARNI prescription compared with not-for-profit hospitals (odds ratio, 2.53; 95% CI, 1.05–6.10; *P*=0.04), and hospitals located in the Western United States had lower odds of ARNI prescription compared with those in the Northeast (odds ratio, 0.33; 95% CI, 0.13–0.84; *P*=0.02).

Conclusions—Relatively few hospital characteristics were associated with ARNI prescription at hospital discharge, in contrast to what has been observed in early adoption in other disease areas. Additional evaluation of barriers to implementing new evidence into heart failure practice is needed. (***J Am Heart Assoc.*** **2019;8:e010484. DOI: 10.1161/JAHA.118.010484.)**



J Am Heart Assoc. 2019;8:e010484. DOI: 10.1161/JAHA.118.010484

HF Management Is Multidimensional

Lifestyle Changes/ Patient Education[a]

- Weight loss
- Smoking cessation
- Low-sodium diet
- Exercise training
- Cardiac rehabilitation
- Medication adherence
- Symptom monitoring
- Self-care

Guideline-Directed HF Therapies[a]-[d]

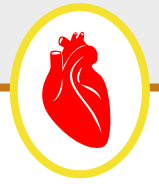
- ACEIs/ARBs
- β-Blockers
- Aldosterone antagonists
- ARNI
- Funny channel inhibition
- HYD/ISDN
- Diuretics
- Digoxin

Devices[a]

- CRT
- ICD
- Ventricular assist devices

Transplantation in Advanced HF[a]

- Gold standard for the treatment of refractory end-stage HF
- 1-year posttransplant survival rate of 88%



Palliative Care[a]

- Access to treatment and end-of-life care
- Control of symptoms, psychological distress, and HRQOL
- Advance directives
- Caregiver support
- Frailty/dementia assessments

- Yancy CW, et al. *Circulation*. 2013;128:e240-e327. b. Yancy CW, et al. *Circulation*. 2016;134:e282-e293. c. Kim Y, et al. *CADTH Issues in Emerging Health Technologies*. 2017;151:1-14. d. Yancy CW, et al. *Circulation*. 2017;136e137-e161.

Potential Impact of Optimal Implementation of Evidence-Based HFrEF Therapies on Mortality in the US

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)
ARNI (replacing ACEI/ARB)	2,287,296	2,287,296 (100)	28,484	(18,230-41,017)
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	-	-	96,480	(53,013-158,514)

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030. and Fonarow GC et al. JAMA Cardiology 2016;1(6)714-717.

CONCLUSIONS

- GWTG-HF is focused on improving on meaningful processes of care and patient-centered outcomes
- ACEI/Beta Blocker/MRA previously established as cornerstone of therapy in HFrEF
- ARNI further reduces morbidity and mortality
- PIONNER-HF provides important need insights into the safety and effectiveness of in-hospital initiation of ARNI in eligible patients
- In-hospital initiation of ARNI and other GDMT improves outcomes
- Every effort should be made to optimize use and dosing of GDMT in all settings in which these patients are cared for

Fonarow GC et al JACC 2017 Oct 10;70(15):1931-1934 and Konstam M et al. JACC: Heart Failure, Volume 4, Issue 1, January 2016, Pages 12-20

American Heart Association.

CONTACT US TO LEARN MORE

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Thank You For Your Active Participation And Contributions To GWTG-Heart Failure!