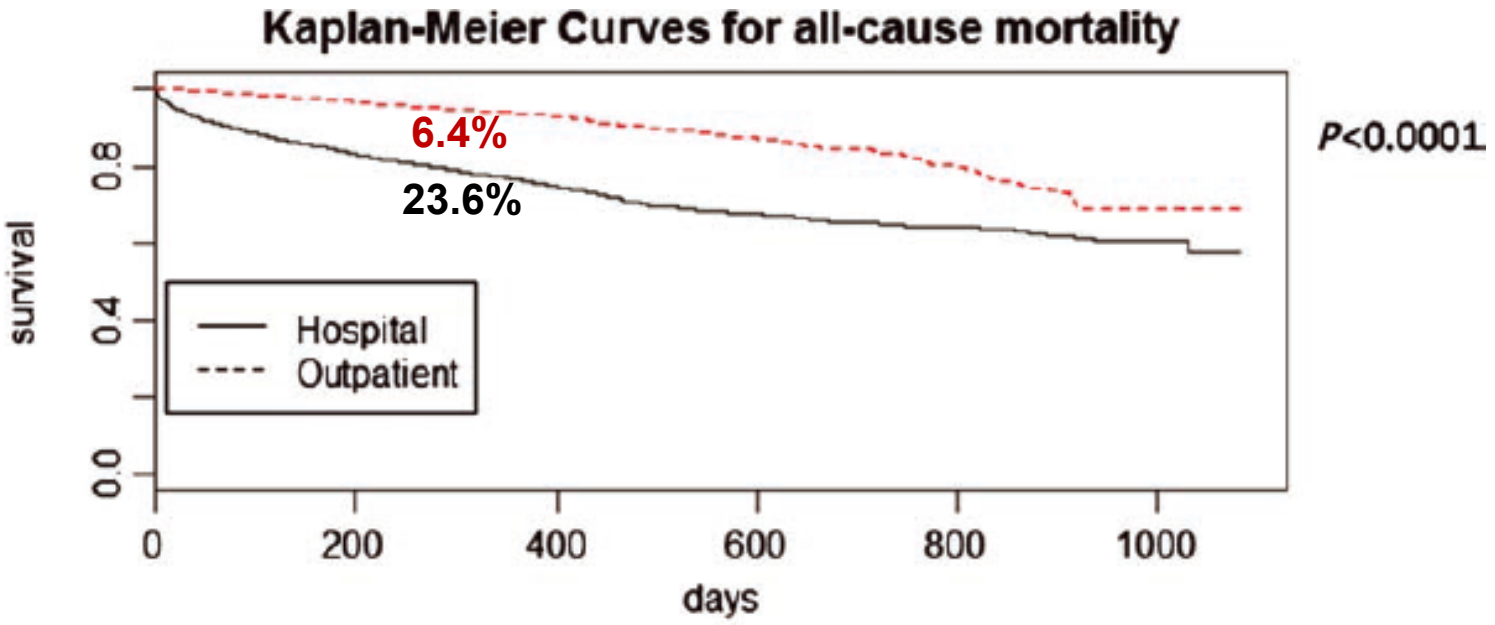
TERAPIA DELLO SCOMPENSO DAI BETA-BLOCCANTI AGLI ARNI (ARNI SI – ARNI NO)

Iseo 10 Novembre 2018

Carlo Lombardi
Cattedra di Cardiologia Università e Spedali Civili di Brescia

All-cause mortality in the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT)

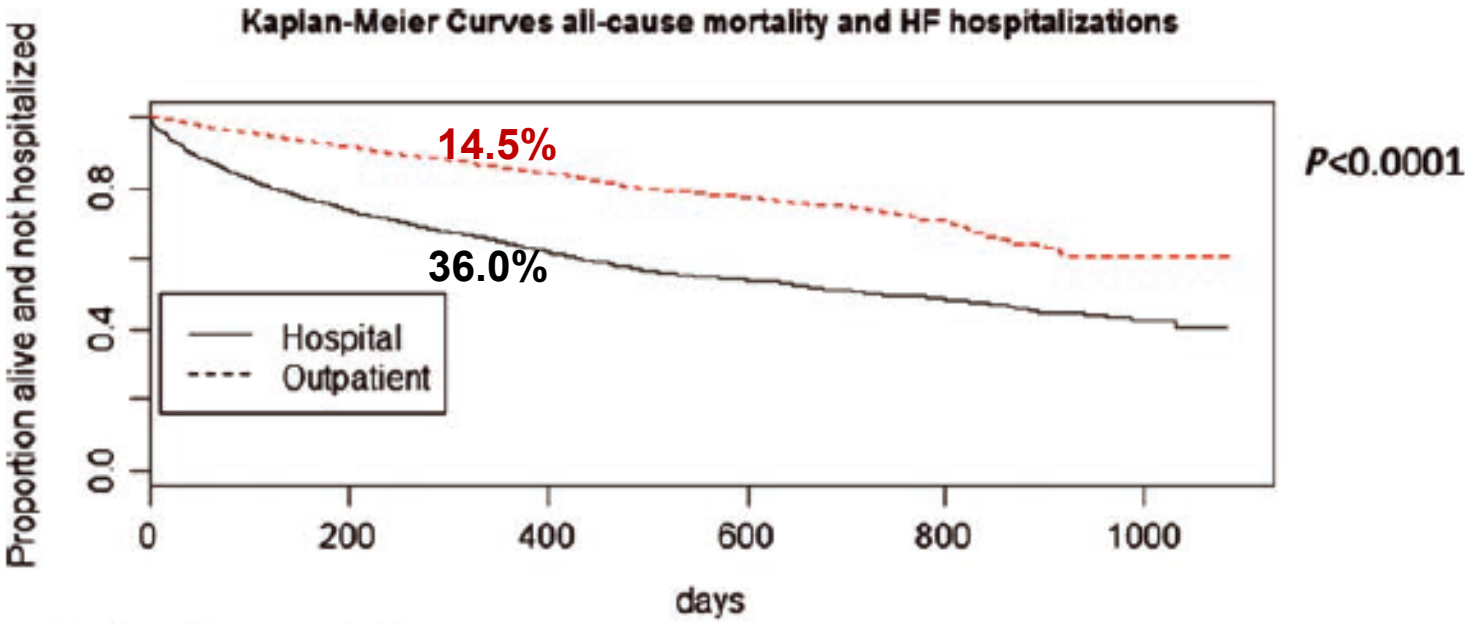


Number of Patients at Risk:

Hospital	5038	3874	1656	763	384	100
Outpatient	7401	6892	2367	700	246	69

Crespo-Leiro et al. Eur J Heart Fail 2016; 18:613-625

All-cause mortality and HF-hospitalizations in the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT)



Number of Patients at Risk:

Hospital	4958	3369	1457	708	336	52
Outpatient	7378	6513	2221	684	242	67

Crespo-Leiro et al. Eur J Heart Fail 2016; 18:613-625

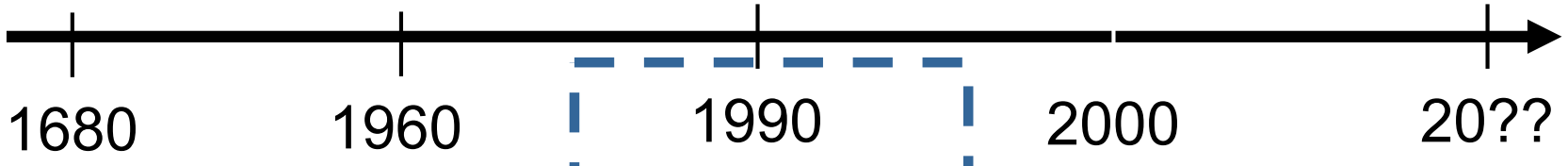
Recent trials in acute heart failure

Class	Drug	Trial	Year	Results
PDE-III inhibitors	Milrinone	OPTIME-CHF	2002	n.s. mortality, ↑ side effects
Ca-sensitizers	Levosimendan	SURVIVE, REVIVE	2007	n.s. outcomes (vs dobutamine) , ↑ side effects (vs placebo)
Endothelin-antagonists	Tezosentan	VERITAS	2007	n.s. dyspnea & outcomes
Vasopressin antagonists	Tolvaptan	EVEREST	2007	Slight ↓dyspnea, n.s. outcomes
Adenosine A1 receptor antagonist	Rolofylline	PROTECT	2010	Slight ↓dyspnea, n.s. outcomes; ↑ seizures
Natriuretic peptides	Nesiritde	ASCEND-AHF	2011	Slight ↓dyspnea ↑ n.s. outcomes
Vasodilatator	Serelaxin	RELAX-AHF	2015	Negative

Current medical treatment of chronic HF: Key evidence (ESC guidelines)

Trial	Drug	Mortality relative risk reduction	Absolute risk reduction	Number needed to treat
2008 Guidelines				
CONSENSUS, 1987	Enalapril	27%	14.6%	7
SOLVD Treatment, 1991	Enalapril	16%	4.5%	22
CIBIS, MERIT-HF, 1999	Bisoprolol metoprolol	34%	4.3%	23
COPERNICUS, 2001	carvedilol	35%	7.1%	14
RALES, 1999	Spironol.	30%	11.4%	9
SENIOR	Nebivolo		14%	
ValHeFT, 2001	Valsartan	24% HF hosp	3.3%*	30*
CHARM-Added, 2003	Candesartan	16%†	4.4%‡	23‡
CHARM-Alt., 2003	Candesartan	23%‡	7%‡	14‡
Added in 2012 Guidelines				
EMPHASIS	Eplerenone	24%	3%	33
SHIFT	Ivabradine	18%‡	4.2%‡	24‡
Added in 2016				
Angiotensin receptor Neprilysin Inhibitor	LCZ696	20%		

"Eras"of Heart Failure Therapy



Cardiorenal

Interventions
- Diuretics
- Digitalis

Hemodynamic

Interventions
- Vasodilators
- Inotropes

Neurohormonal

Interventions
- ACE-I
- β-Blockers
- ARBs
- Aldosterone Antagonists
- HDZ/Isosorbide
- ARNI
- Neuromodulation

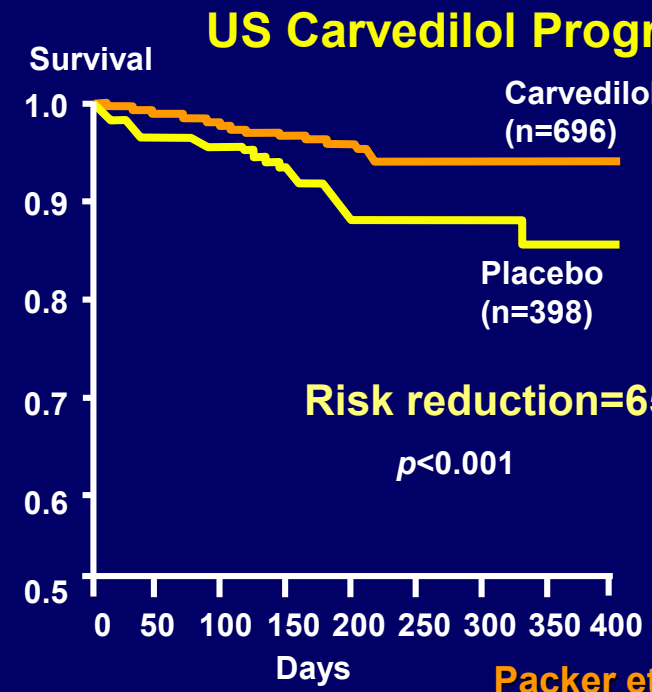
Biomechanical

Interventions
- ICDs
- CRT
- CSD
- LVAD
- Repair and Regeneration
- Metabolism

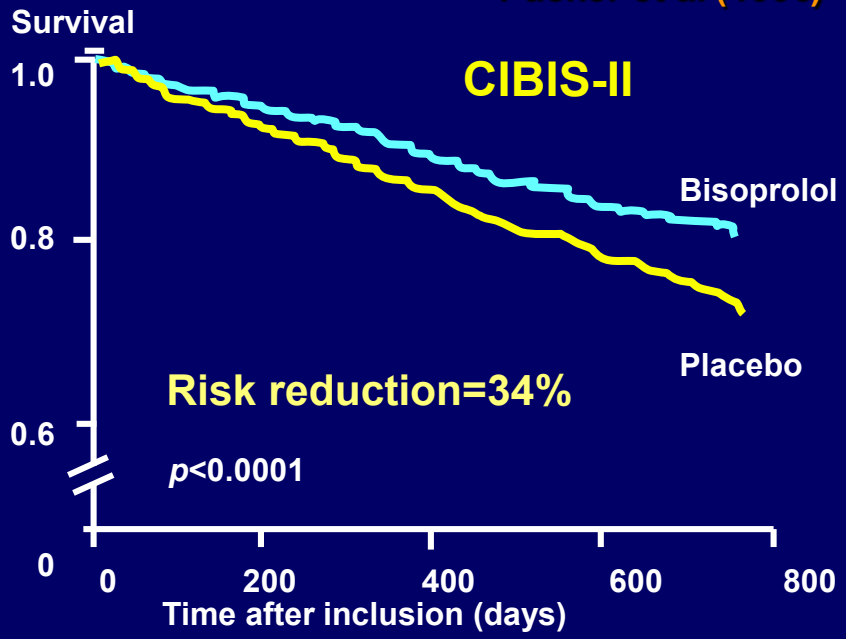
Personalized

Interventions
- Genomics
- Proteomics
- Biomarkers
- Imaging
- Biosensors

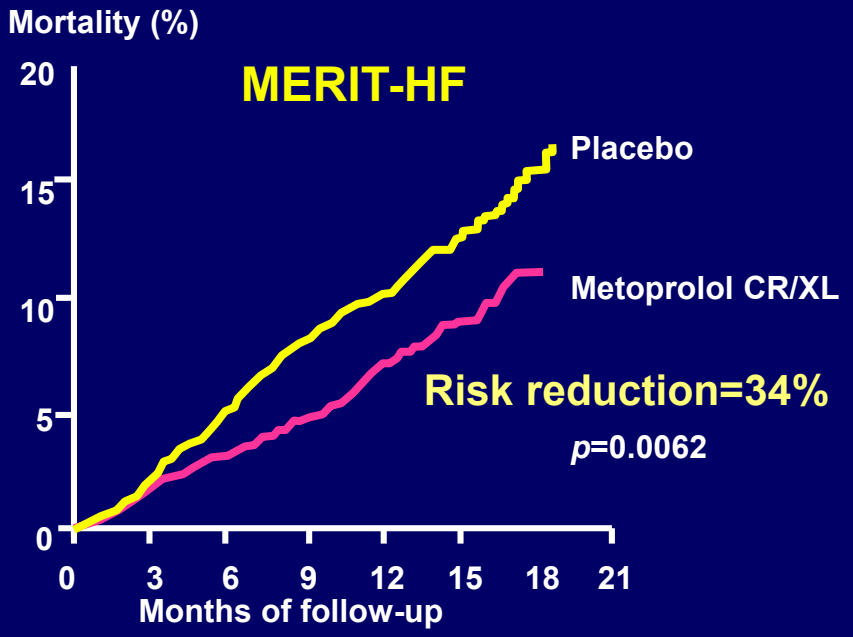
β blockers in Mild to Moderate HF – all-cause mortality



Packer et al (1996)

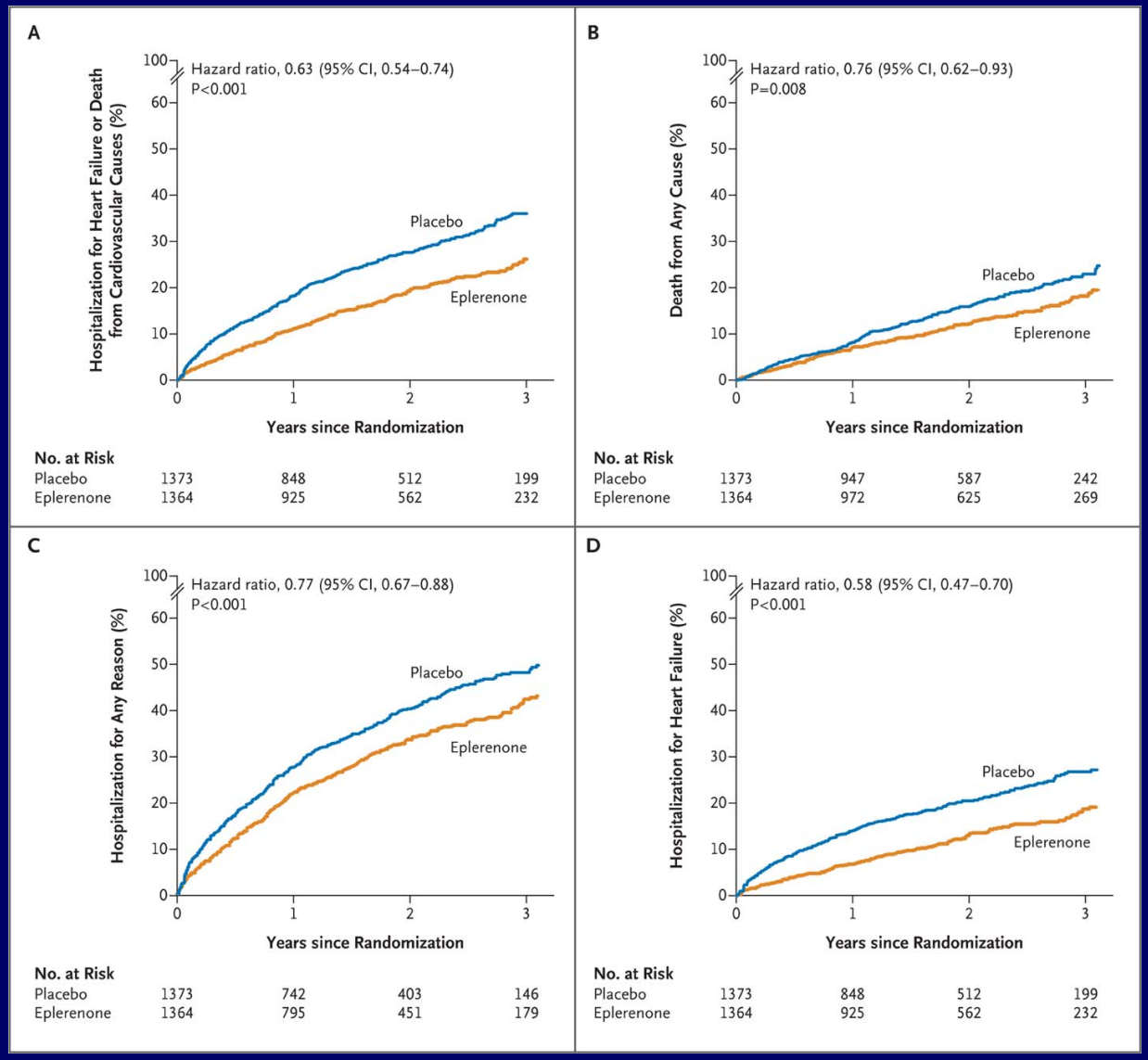


CIBIS-II Investigators (1999)



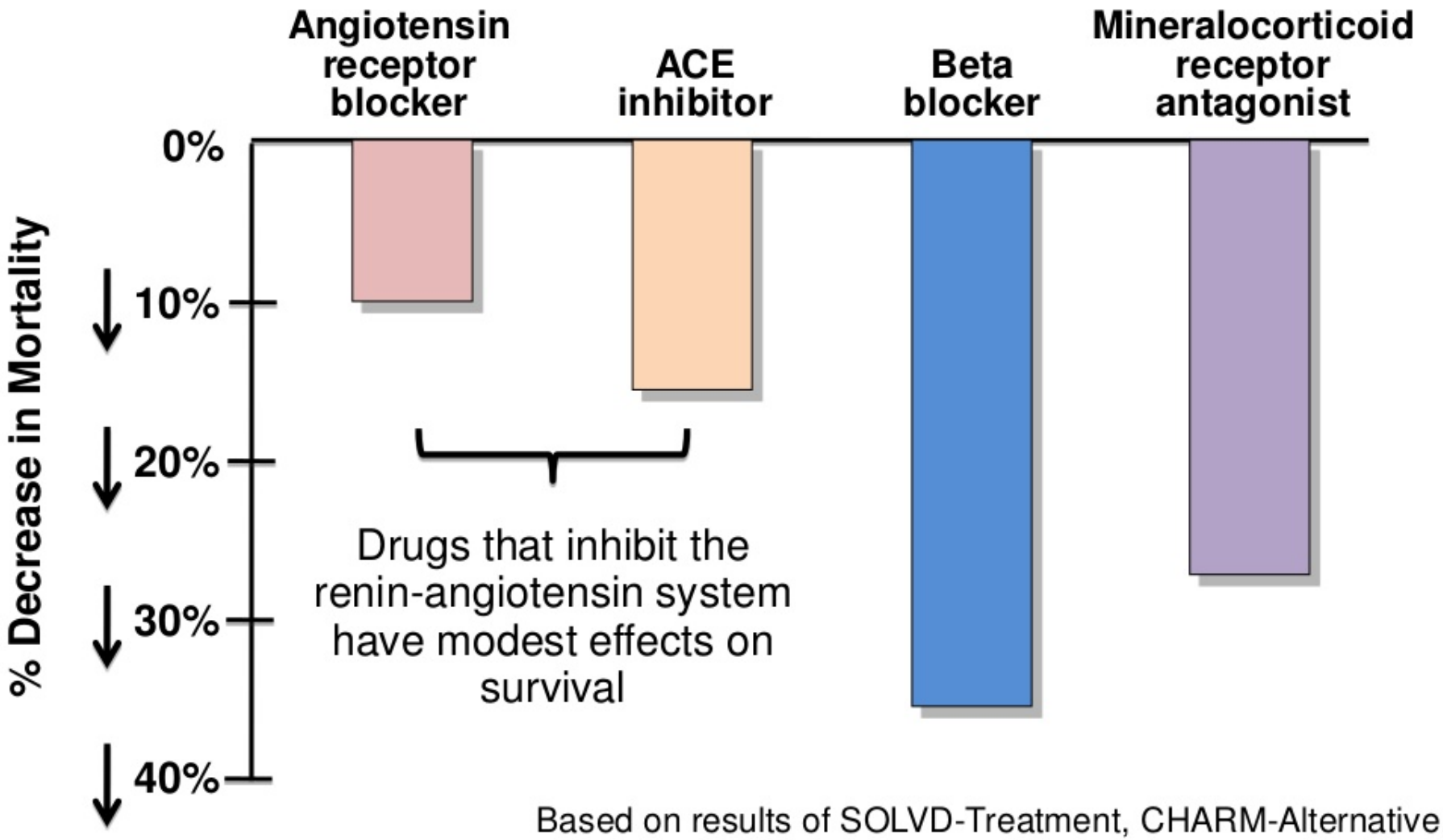
The MERIT-HF Study Group (1999)

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



Zannad F et al. N Engl J Med 2011;364:11-21

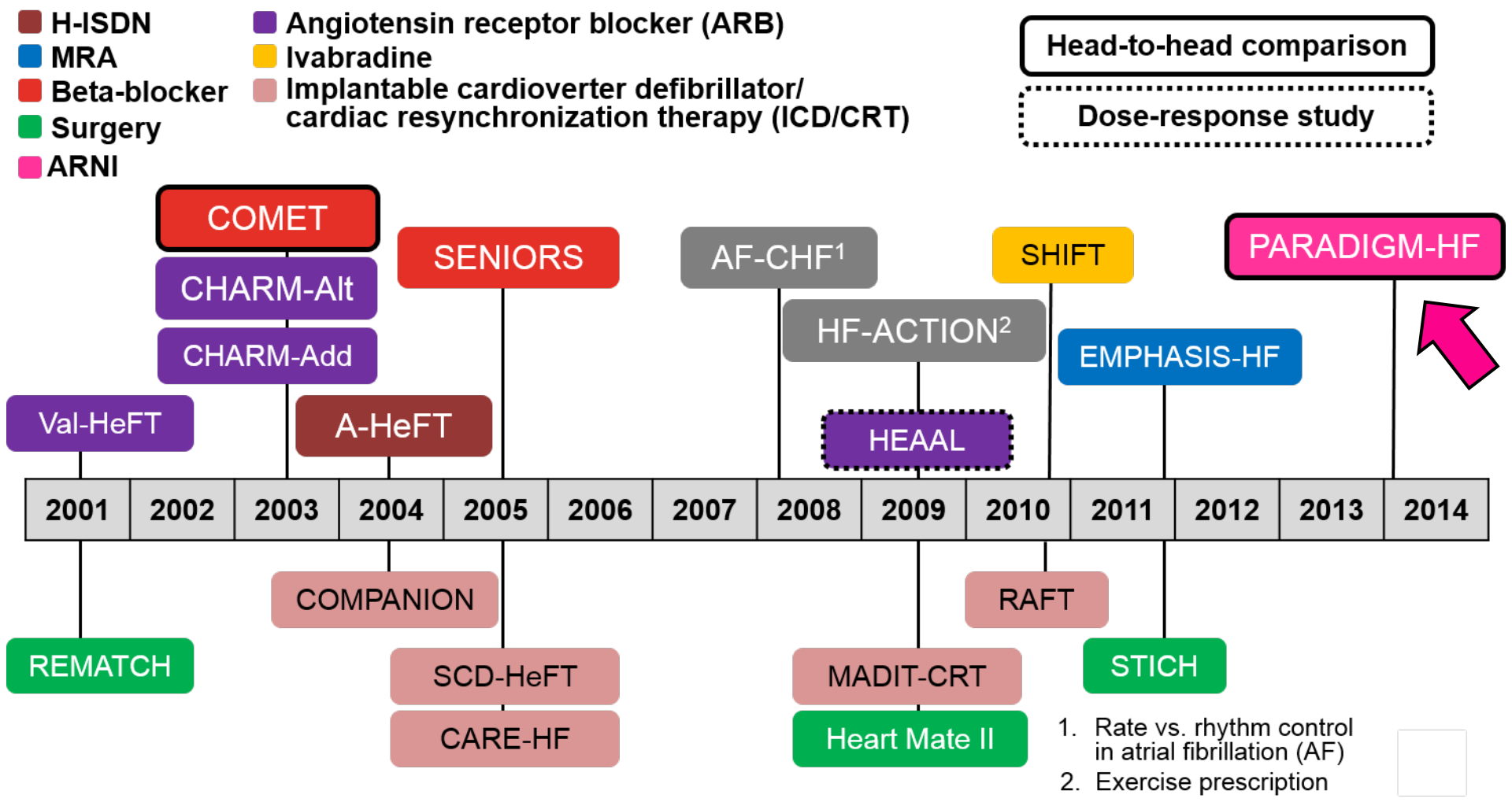
Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction



Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Thirty years of progress in HF-rEF

Positive drug, device and other trials 2001-2014

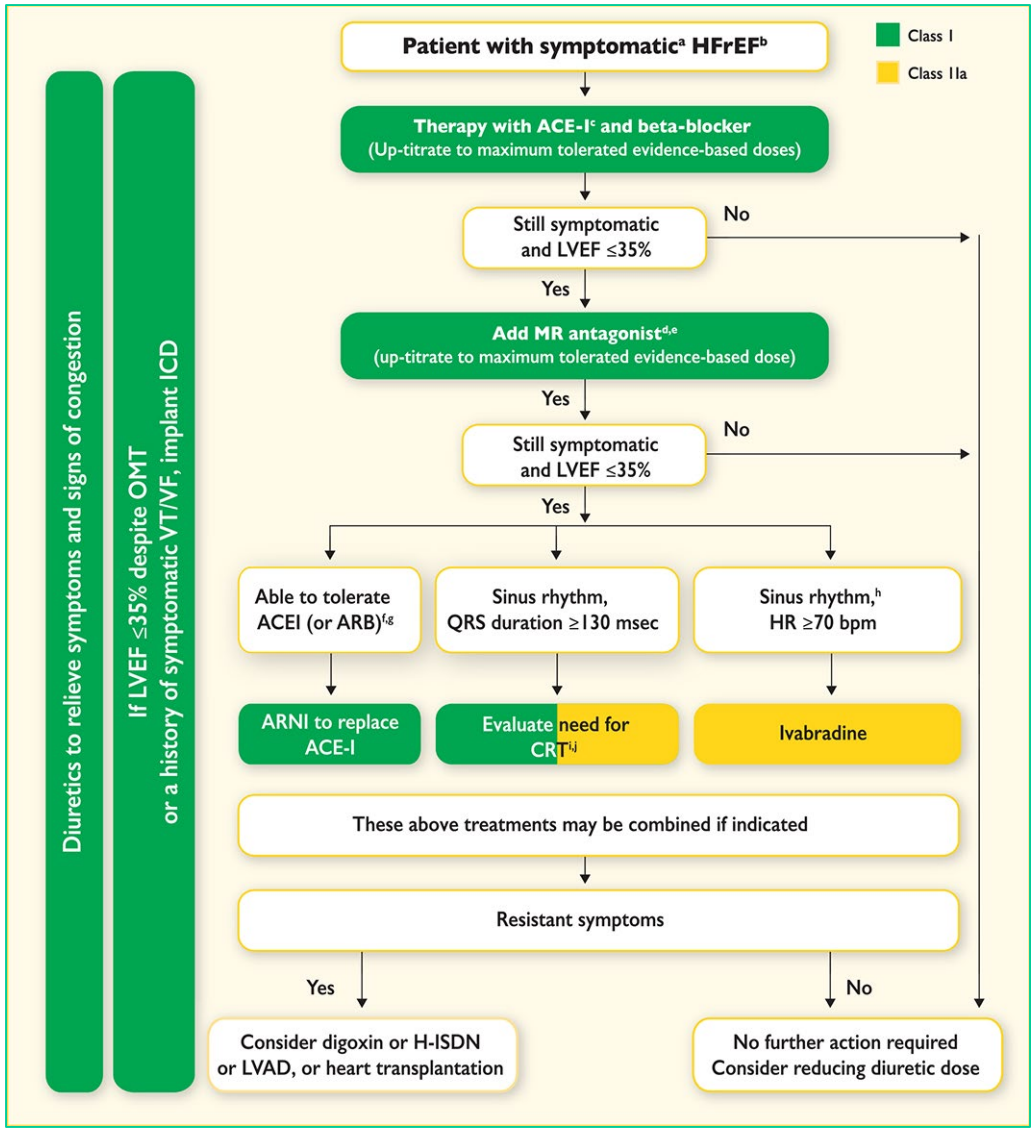


Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
An ACE-I[d] is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A	2, 163–165
A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A	167–173
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I[d] and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A	174, 175

Linee Guida ESC 2016

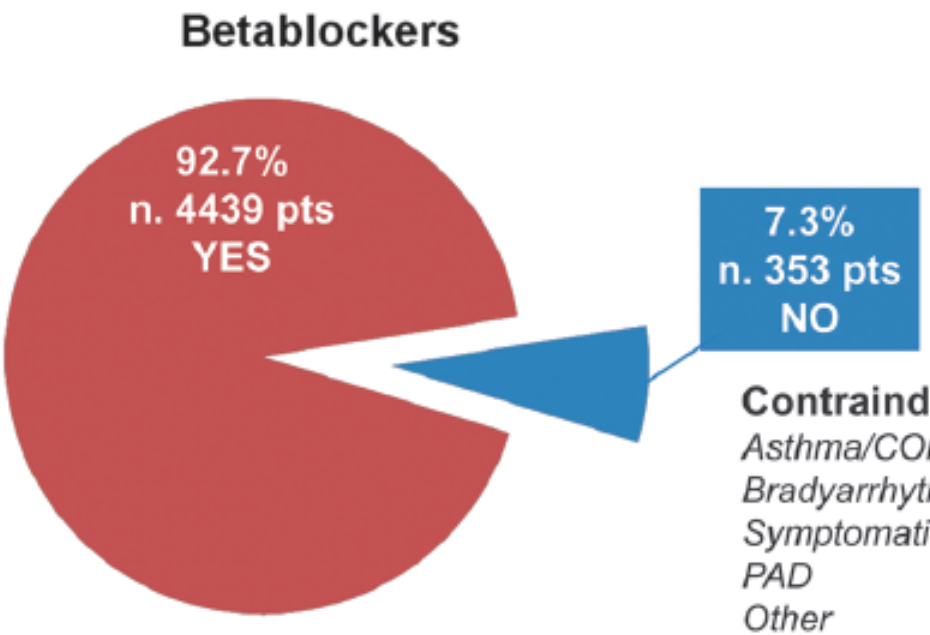
Therapeutic algorithm for a patient with symptomatic HFrEF



Ponikowski et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

Beta-Blocker Treatment in the ESC-HF Long-Term Registry

B

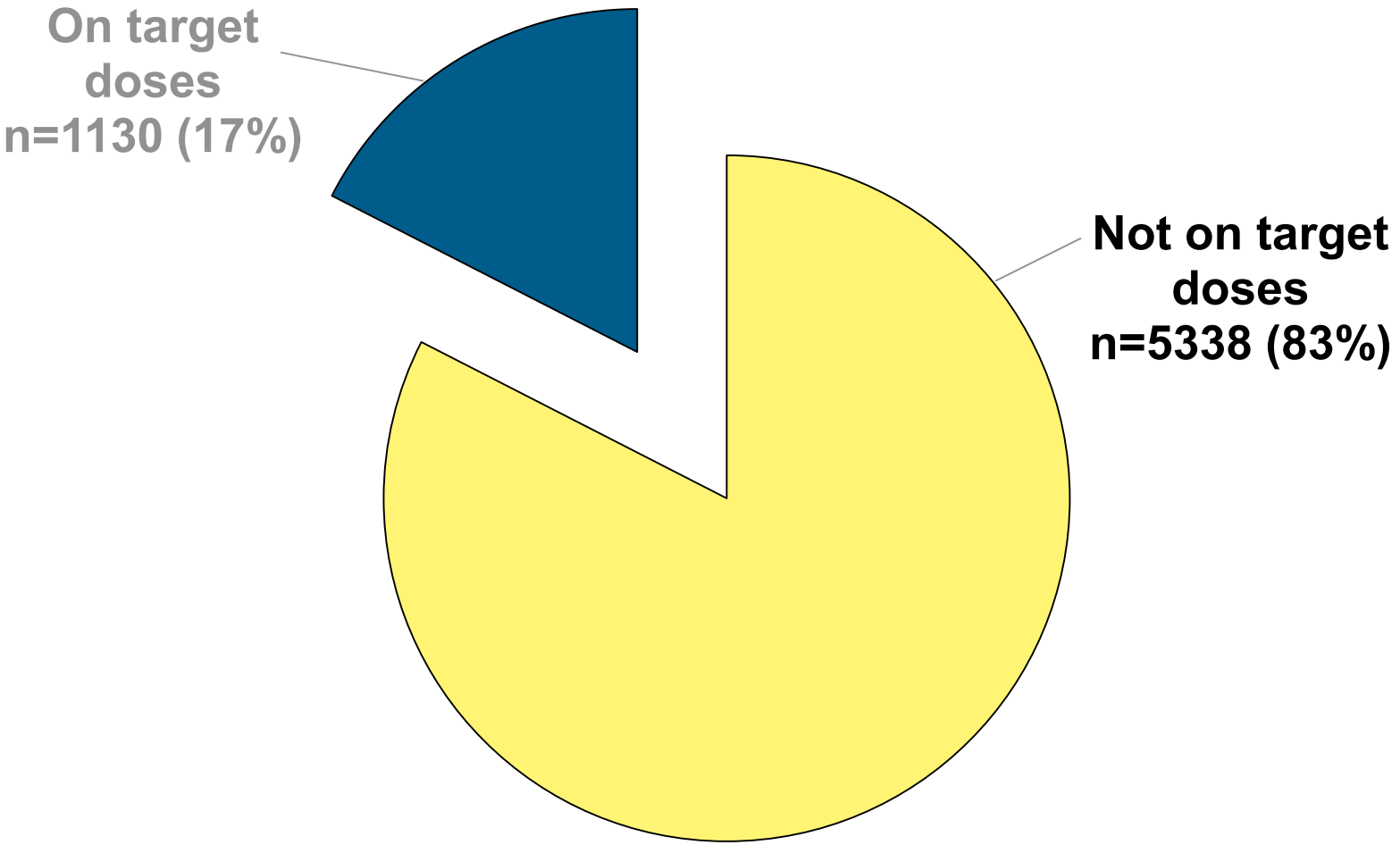


Contraindicated	**n. 78 (1.6%)**
Asthma/COPD	*n. 28 (35.9%)*
Bradyarrhythmia	*n. 11 (14.1%)*
Symptomatic hypotension	*n. 11 (14.1%)*
PAD	*n. 3 (3.8%)*
Other	*n. 25 (32.1%)*
Not tolerated	**n. 165 (3.4%)**
Bronchospasm	*n. 39 (23.6%)*
Symptomatic hypotension	*n. 46 (27.9%)*
Bradyarrhythmia	*n. 22 (13.3%)*
Worsening HF	*n. 36 (21.8%)*
Other	*n. 22 (13.3%)*
Real undertreatment	**n. 110 (2.3%)**

COPD=chronic obstructive pulmonary disease; HF=heart failure; PAD=peripheral artery disease

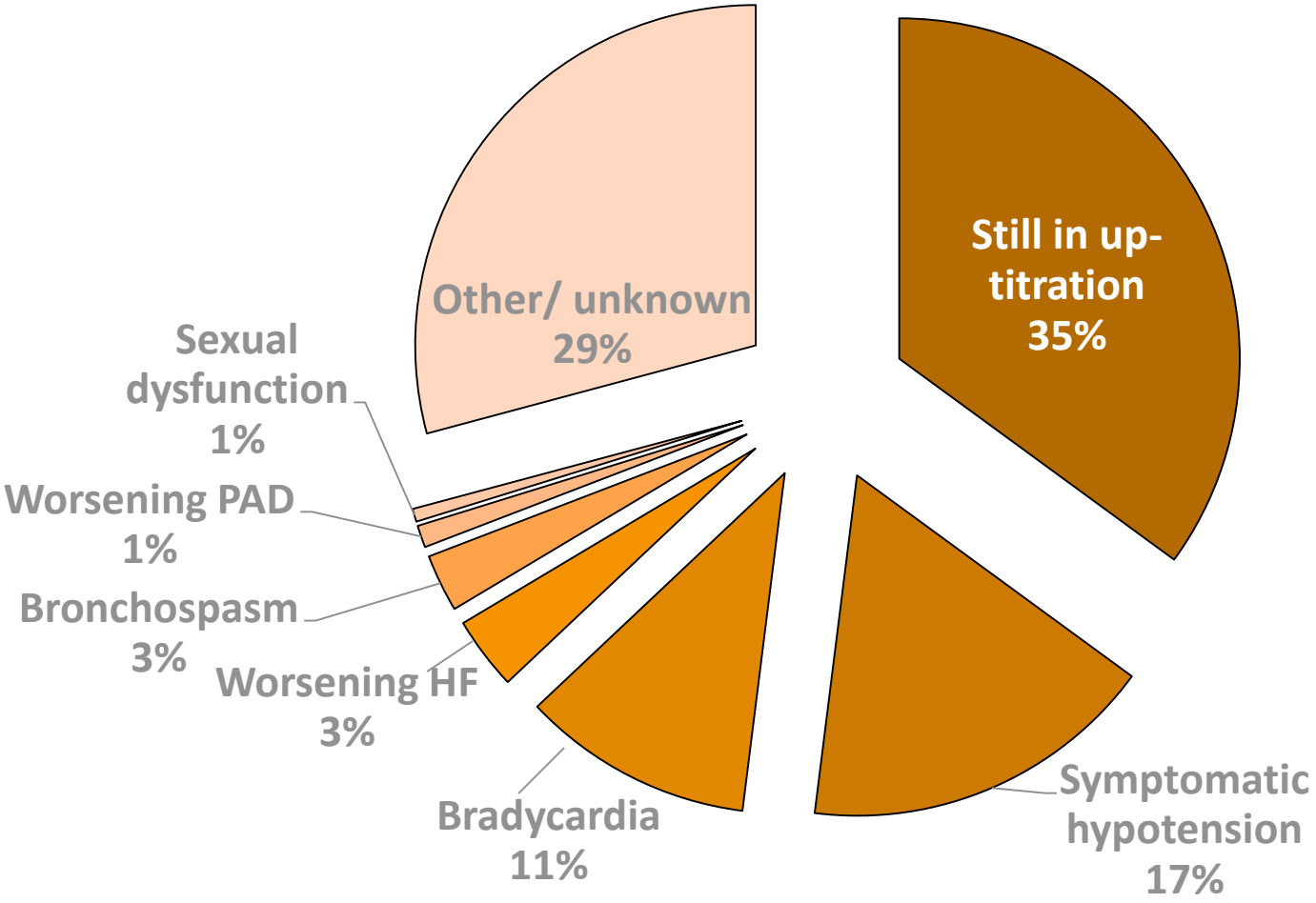
Maggioni AP, et al. *Eur J Heart Fail*. 2013;15:1173-1184.

Patients at Target Doses of Beta-Blocker: ESC-HF Long-Term Registry



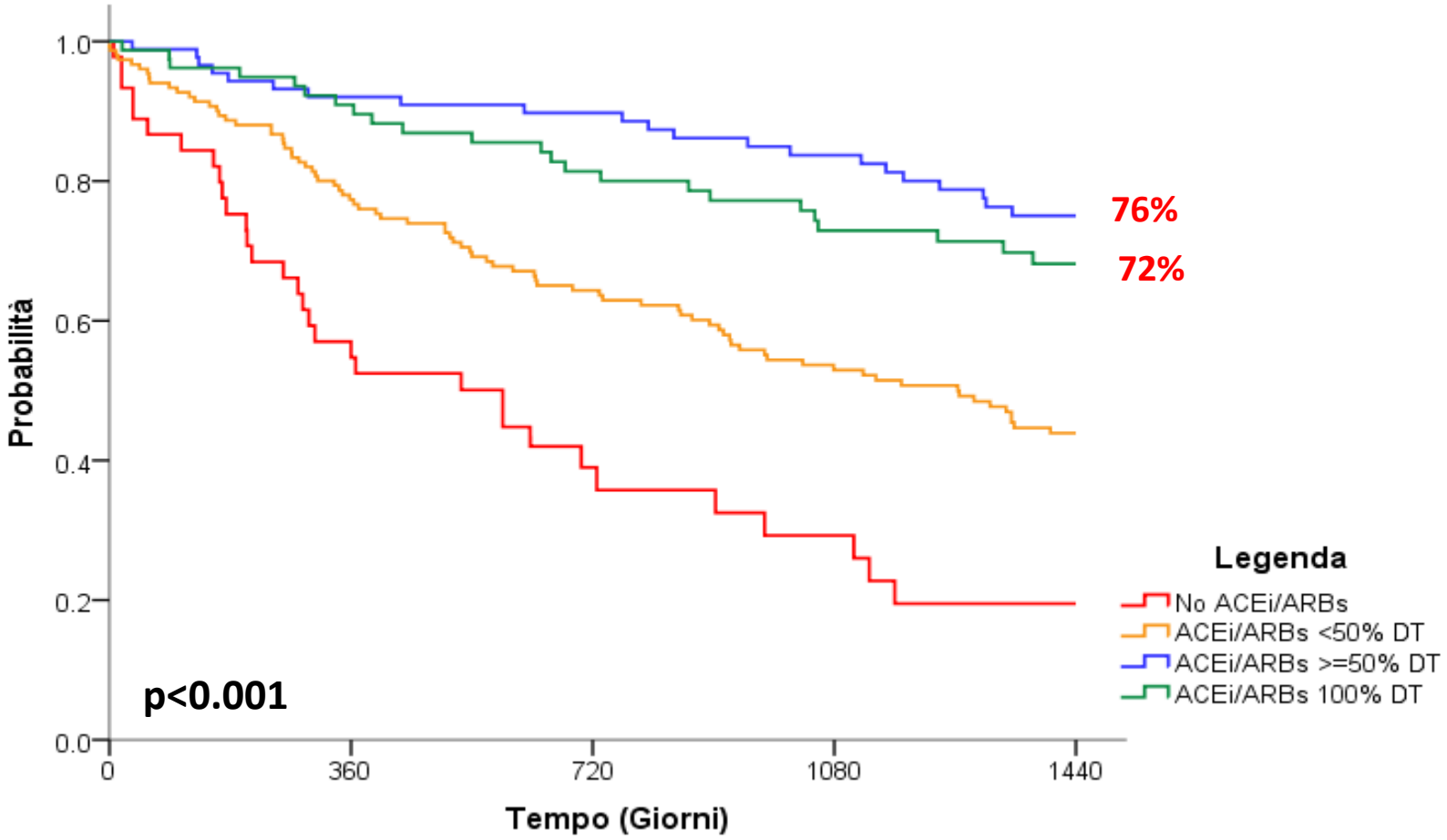
Maggioni AP, et al. *Eur J Heart Fail*. 2013;15(10):1173-1184.

Reasons for Not at Target Beta-Blocker Doses



Maggioni AP, et al. *Eur J Heart Fail*. 2013;15(10):1173-1184.

Morte per tutte le cause e ospedalizzazione per scompenso cardiaco a 4 anni in pazienti con EF ≤40%



The NEW ENGLAND JOURNAL of MEDICINE

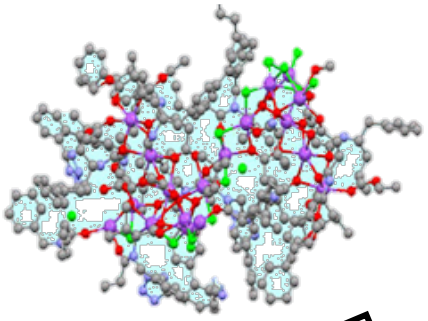
ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

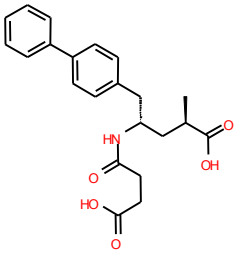
John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

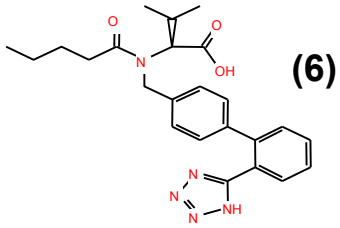
Angiotensin Receptor Neprilysin Inhibitor (ARNI)

LCZ696



(6)



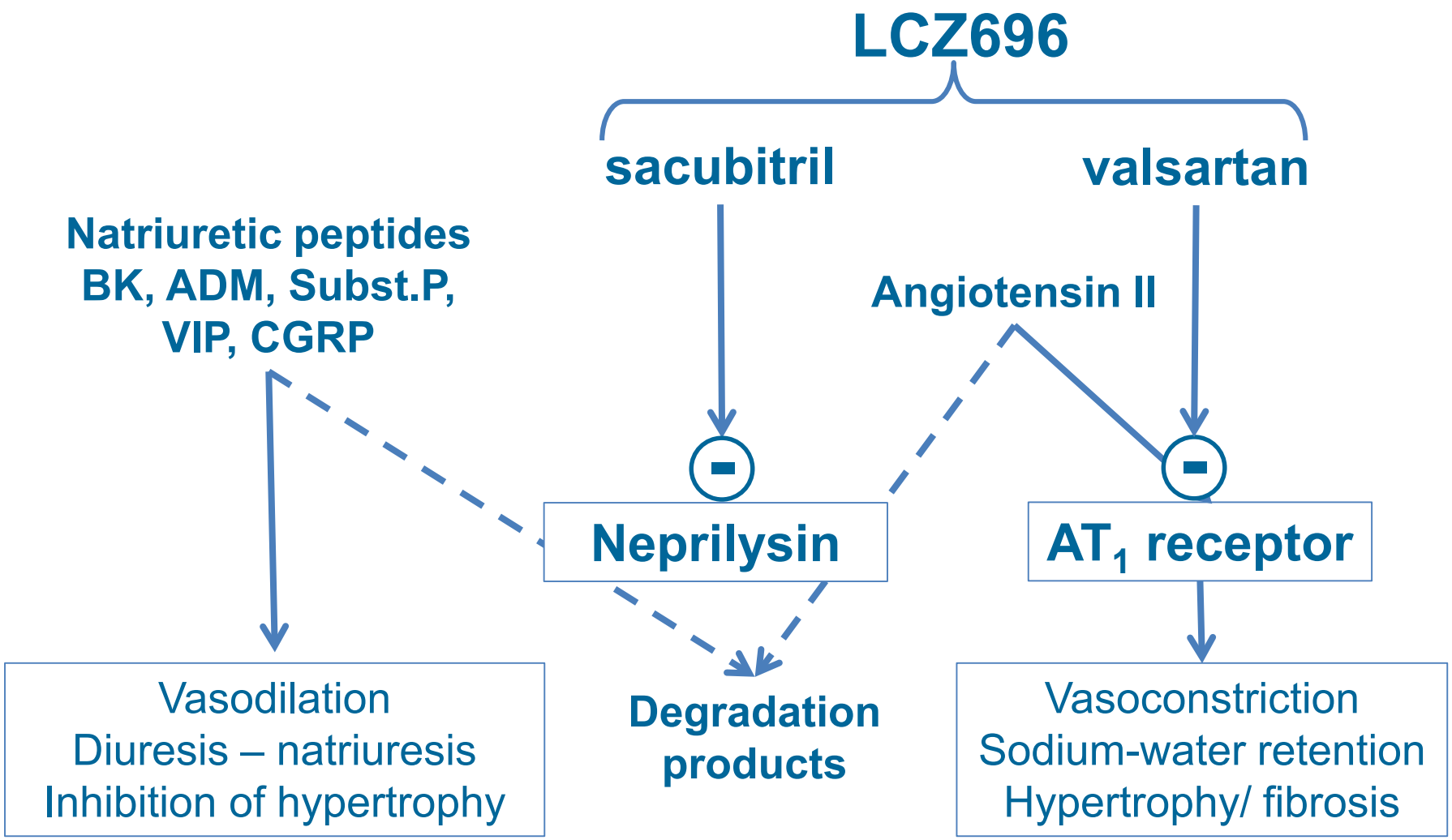


(6)

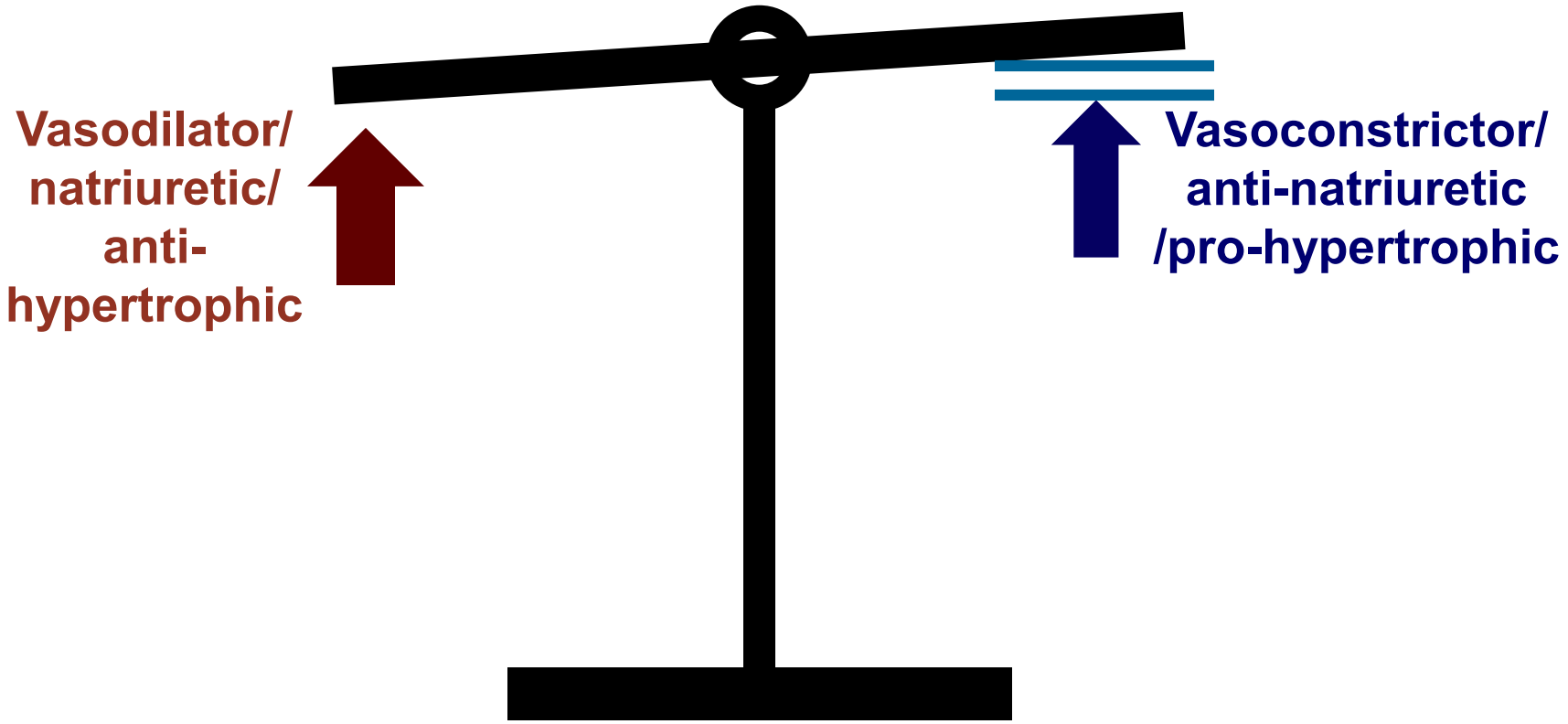
Sacubitril → **LBQ657**

Valsartan

Neprilysin a “promiscous enzyme” breaking down Natriuretic Peptides and Angiotensin II



Heart failure. Now a rationale for neurohormonal modulation



PARADIGM-HF: key inclusion criteria

- Chronic HF NYHA FC II–IV with LVEF ≤35%*
- BNP (or NT-proBNP) levels as follows:
  - ≥150 (or ≥600 pg/mL), or
  - ≥100 (or ≥400 pg/mL) and a hospitalization for HFrEF within the last 12 months
- ≥4 weeks' stable treatment with an ACEI or an ARB#, and a β-blocker
- Aldosterone antagonist should be considered for all patients (with treatment with a stable dose for ≥4 weeks, if given)

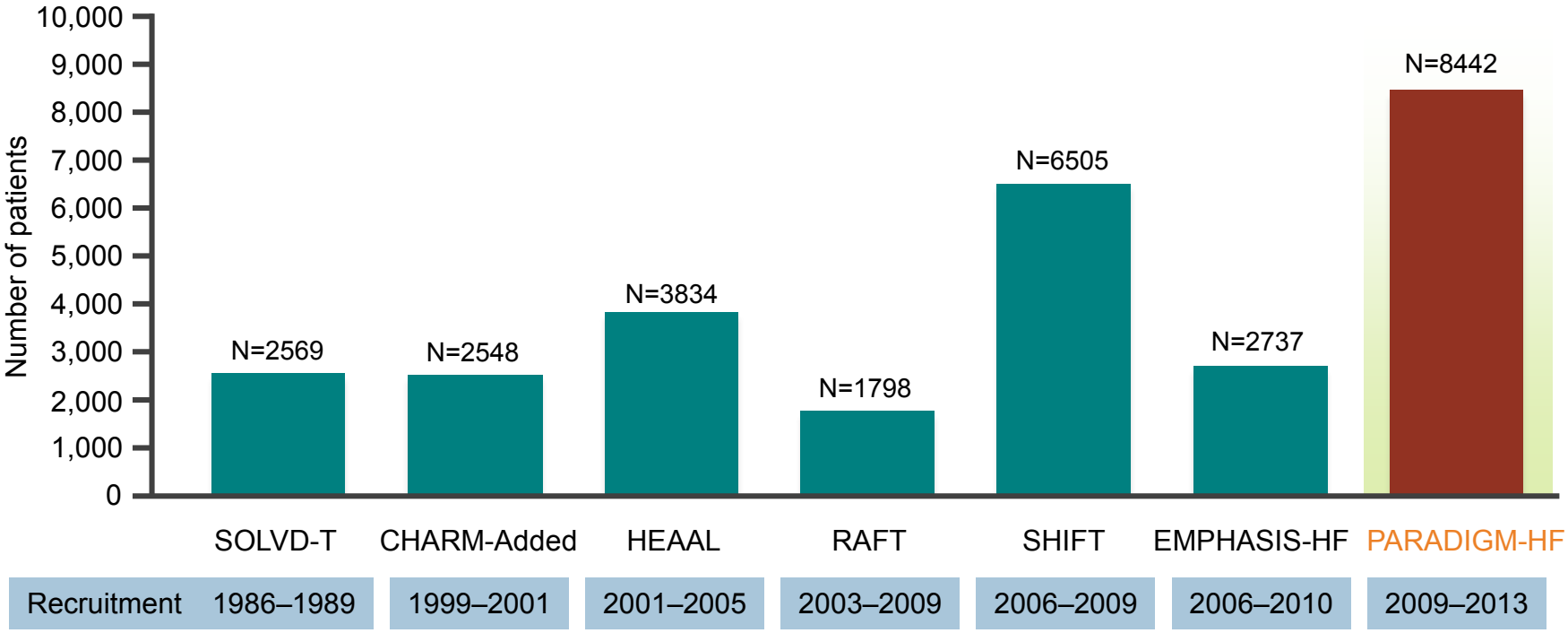
**The ejection fraction entry criteria was ≤40% in the original protocol ; #Dosage equivalent to enalapril ≥10 mg/day*

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BNP: B-type natriuretic peptide; FC: functional class; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

McMurray et al. Eur J Heart Fail. 2013;15:1062–73

PARADIGM-HF

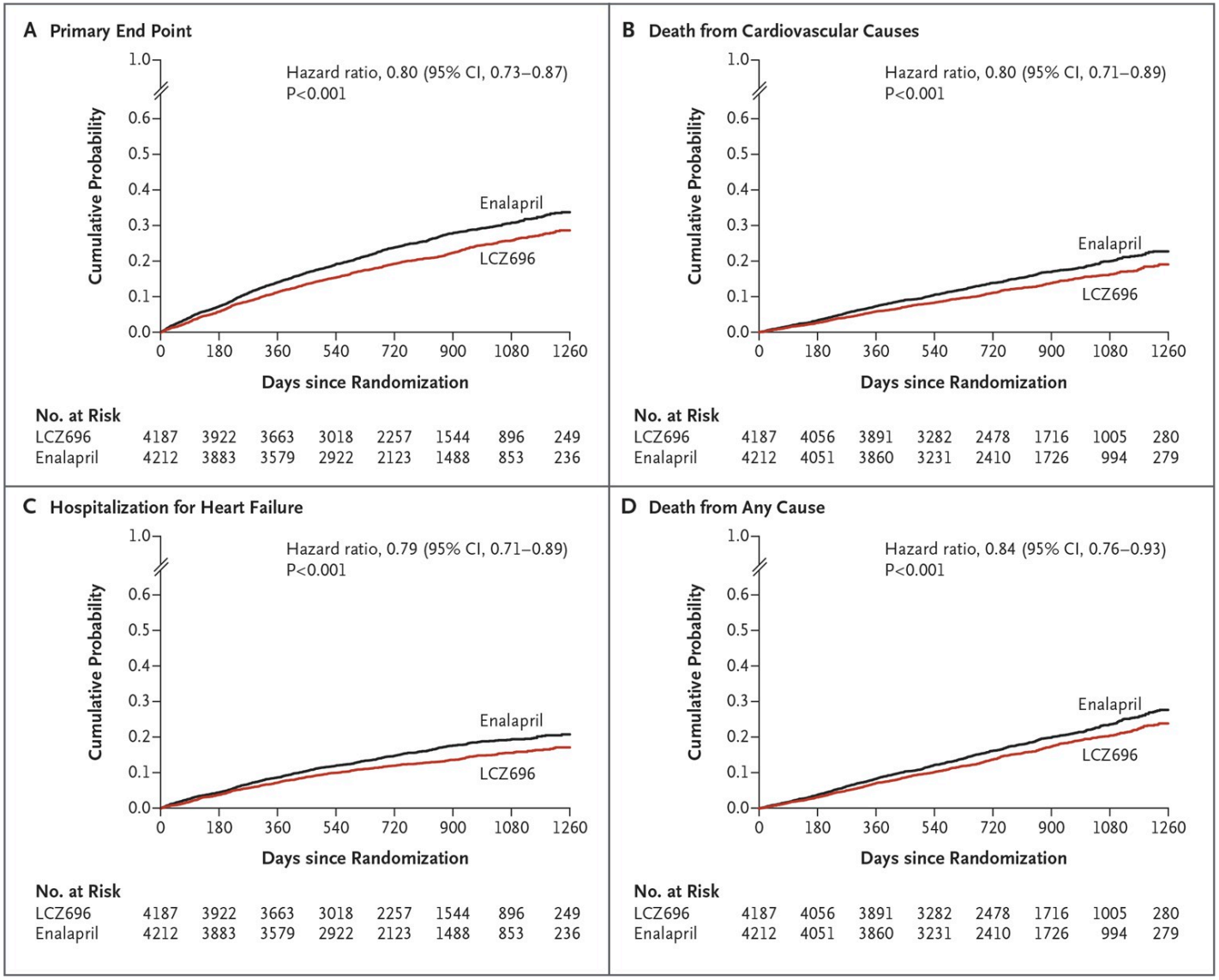
The largest mortality-morbidity trial in patients with HFrEF



CHARM-Added=Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Added trial; EMPHASIS-HF=Eplerenone in Mild Patients Hospitalization And Survival study in Heart Failure; HEAAL=Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan; HFrEF=heart failure with reduced ejection fraction; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; RAFT=Resynchronization/Defibrillation for Ambulatory Heart Failure Trial; SHIFT=Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial; SOLVD-T=Studies of Left Ventricular Dysfunction Treatment trial

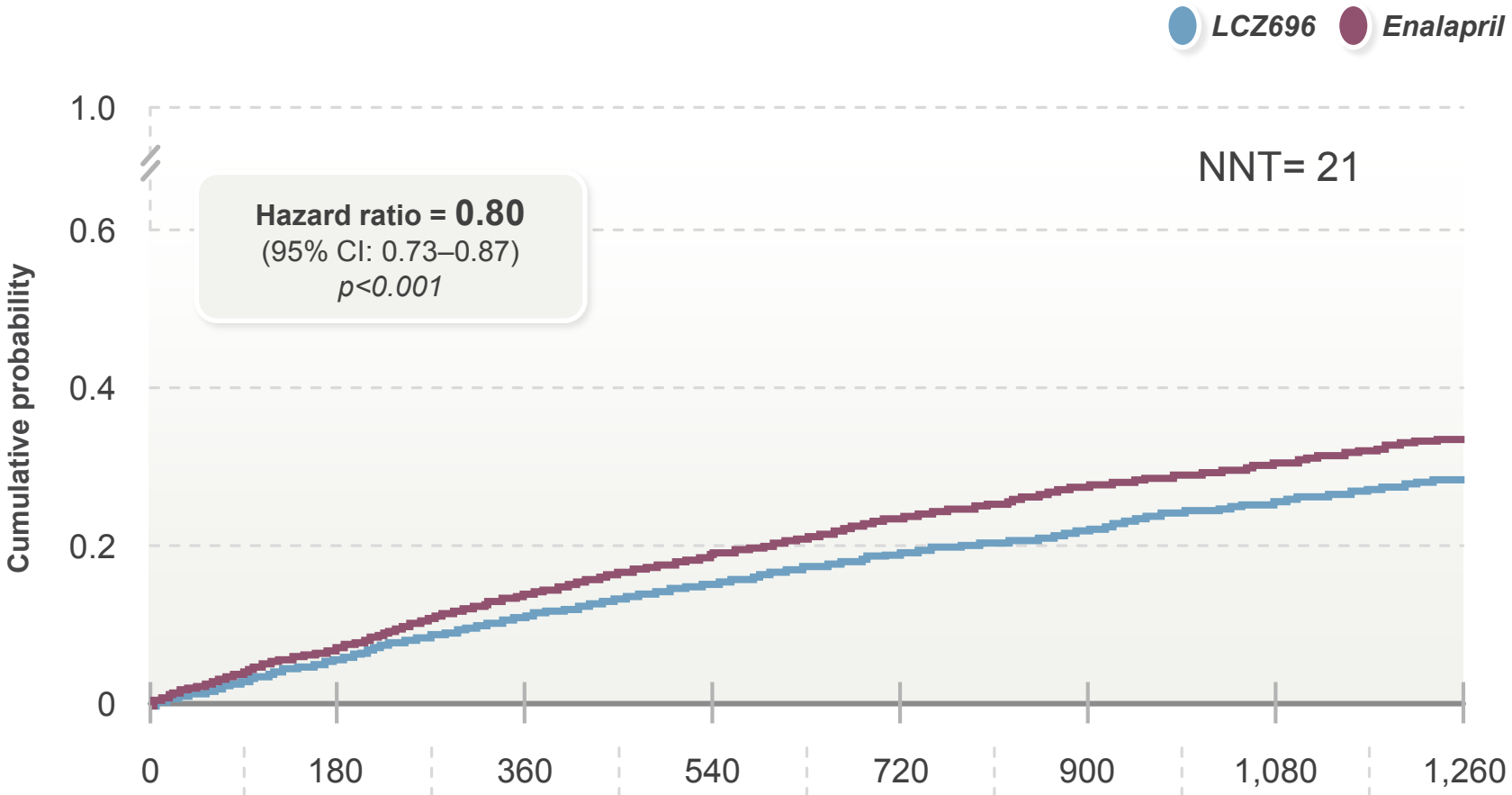
McMurray et al. Eur J Heart Fail 2014;16:817–25

Kaplan–Meier Curves for Key Study Outcomes, According to Study Group



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

Primary endpoint: death from CV causes or first hospitalization for HF

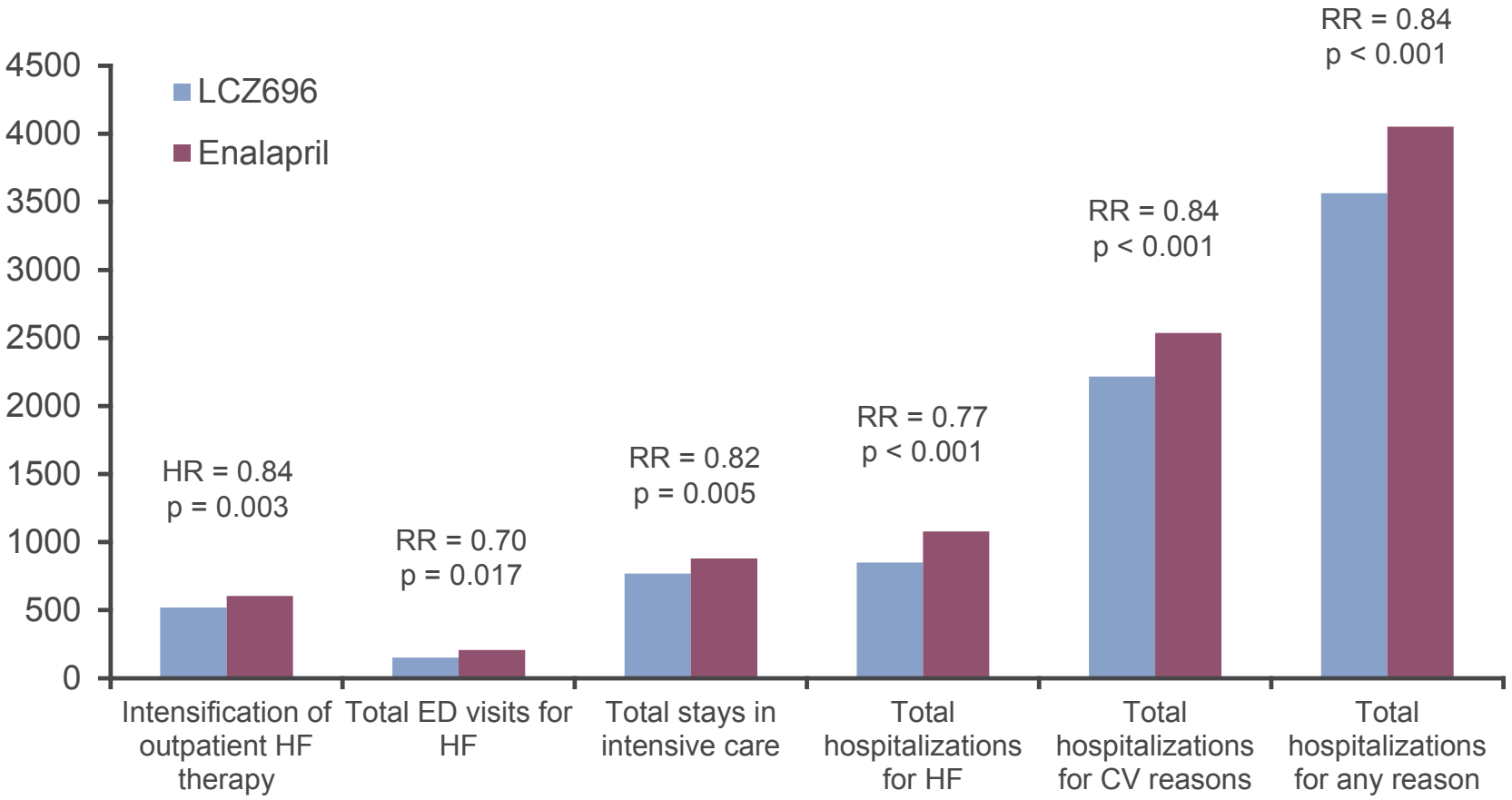


No. at risk								
LCZ696	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

CI: confidence interval; CV: cardiovascular; HF: heart failure

McMurray et al. N Engl Med 2014;371:993–1004.

In patients who were alive, LCZ696 was also superior to enalapril in reducing:



HF = heart failure; ED = emergency department;
CV = cardiovascular

Packer et al. Circulation 2015;131:54–61

Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril in chronic heart failure. Effects on clinical progression in surviving patients with HF

Time to first HF hospitalization in the first 30 days after discharge

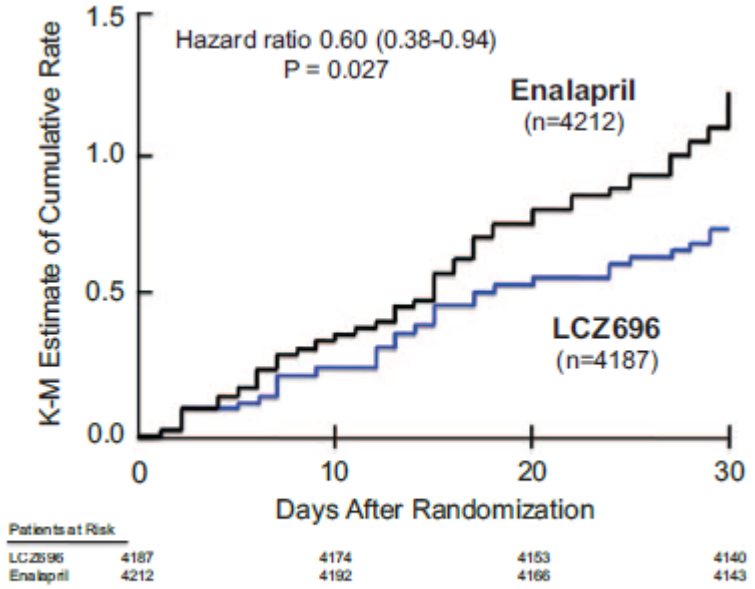


Figure 1. Kaplan–Meier curve for the time to first hospitalization for heart failure during first 30 days after randomization,

Cumulative number of HF hospitalizations per 100 patients

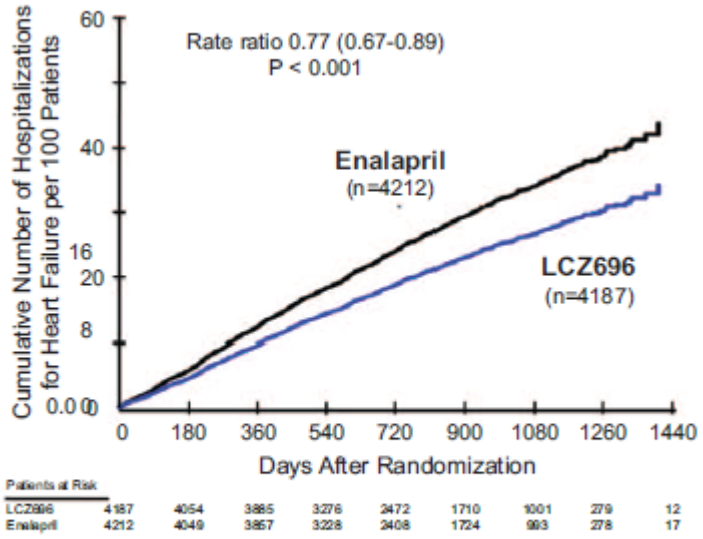


Figure 2. Cumulative number of hospitalizations for heart failure in the enalapril and LCZ696 groups per 100 patients. Shown is the cumulative number of hospitalizations for heart failure in the

Packer et al. Circulation. published online November 17, 2014;

Adverse Events during Randomized Treatment.

Table 3. Adverse Events during Randomized Treatment.*

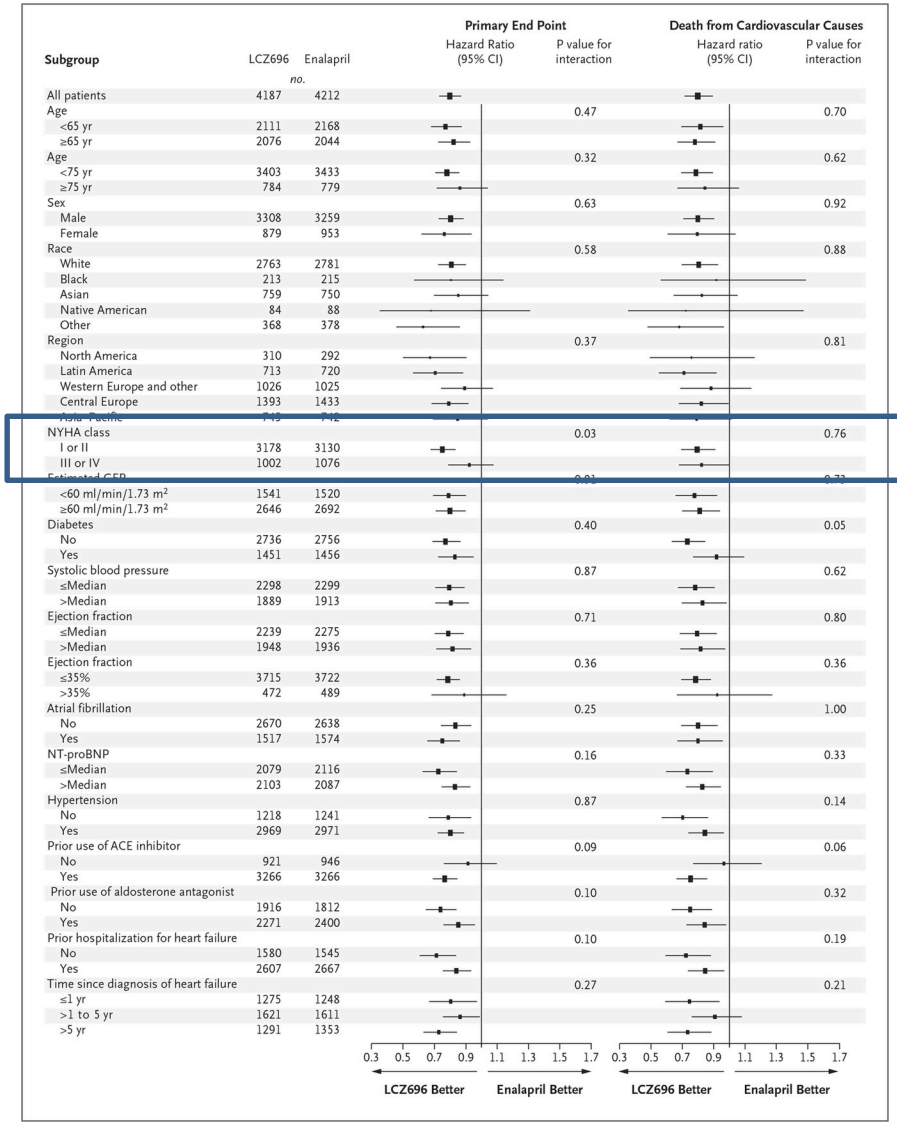
Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P=0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P=0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P=0.56).

† Angioedema was adjudicated in a blinded fashion by an expert committee.

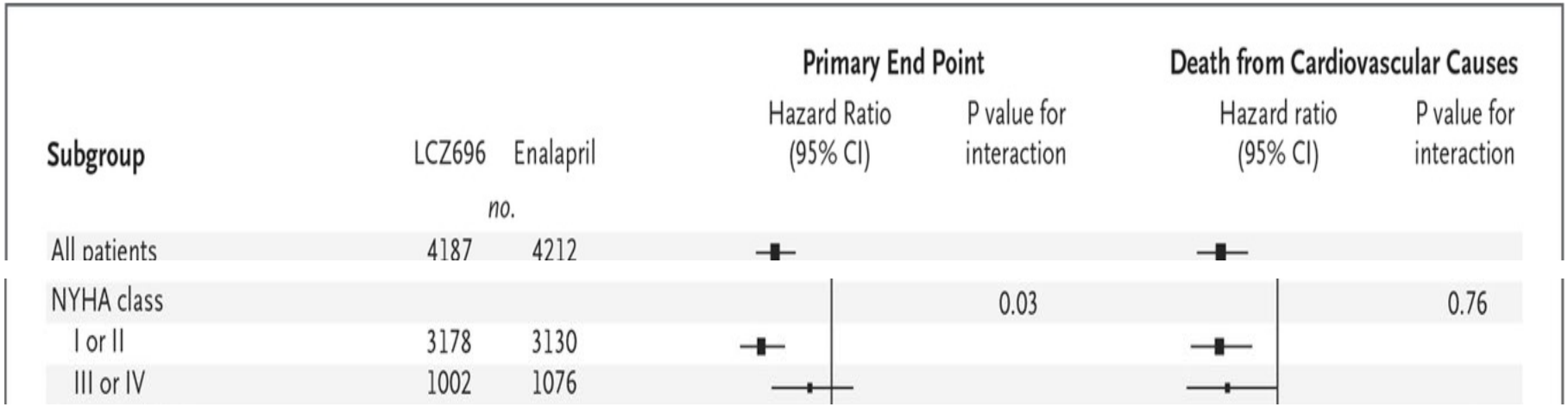
McMurray JJV et al. N Engl J Med 2014;371:993-1004

Prespecified Subgroup Analyses



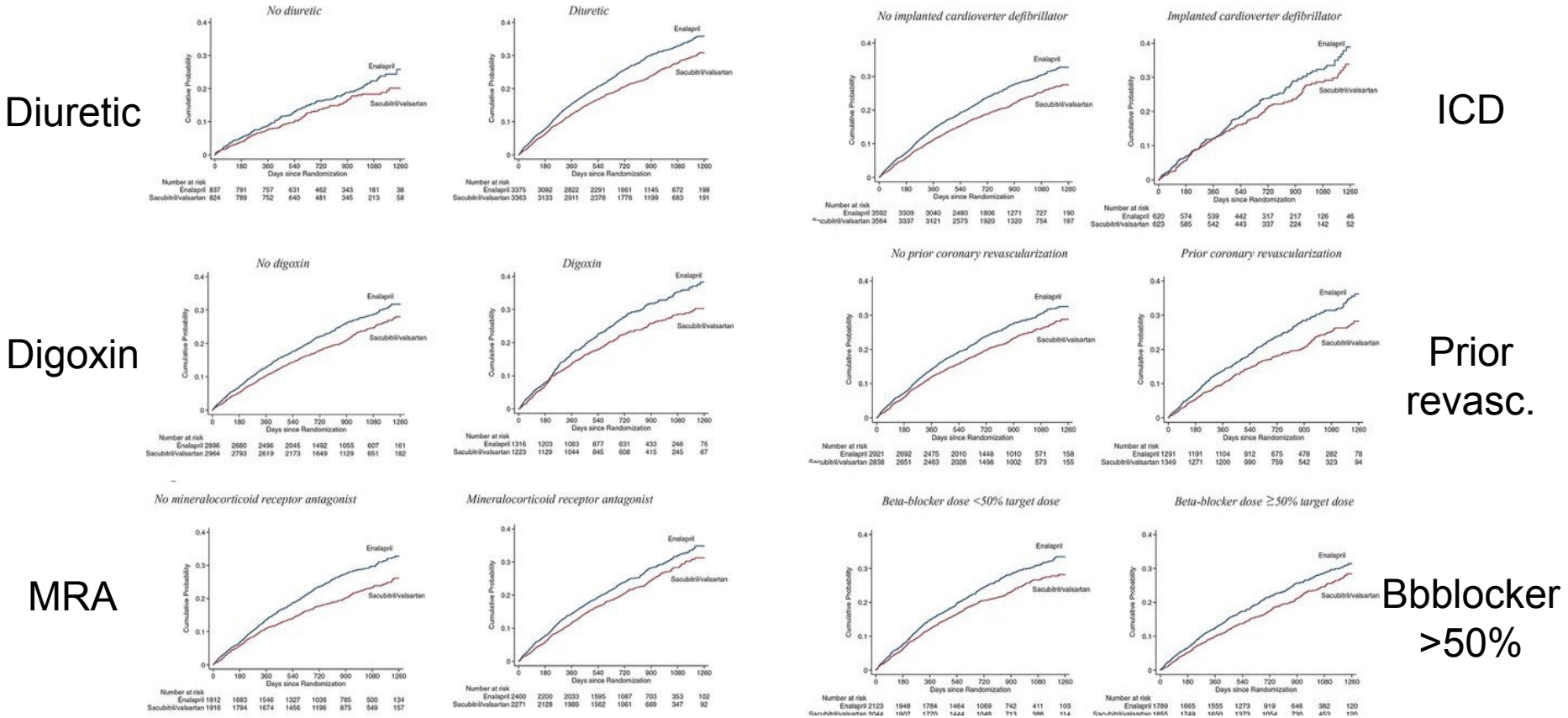
McMurray JJV et al. N Engl J Med 2014;371:993-1004

Prespecified Subgroup Analyses



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

Cumulative incidence of the primary end according to background treatment



Naoki Okumura et al. Circ Heart Fail. 2016;9:e003212

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.592

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Recommendations	Class [a]	Level [b]	Ref [c]
Angiotensin receptor neprilysin inhibitor			
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B	162

[d]Patient should have elevated natriuretic peptides (plasma BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalization within the last 12 months, plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL) and able to tolerate enalapril 10 mg *b.i.d.*

Ponikowski et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

European Journal of Heart Failure (2017)
doi:10.1002/ejhf.788

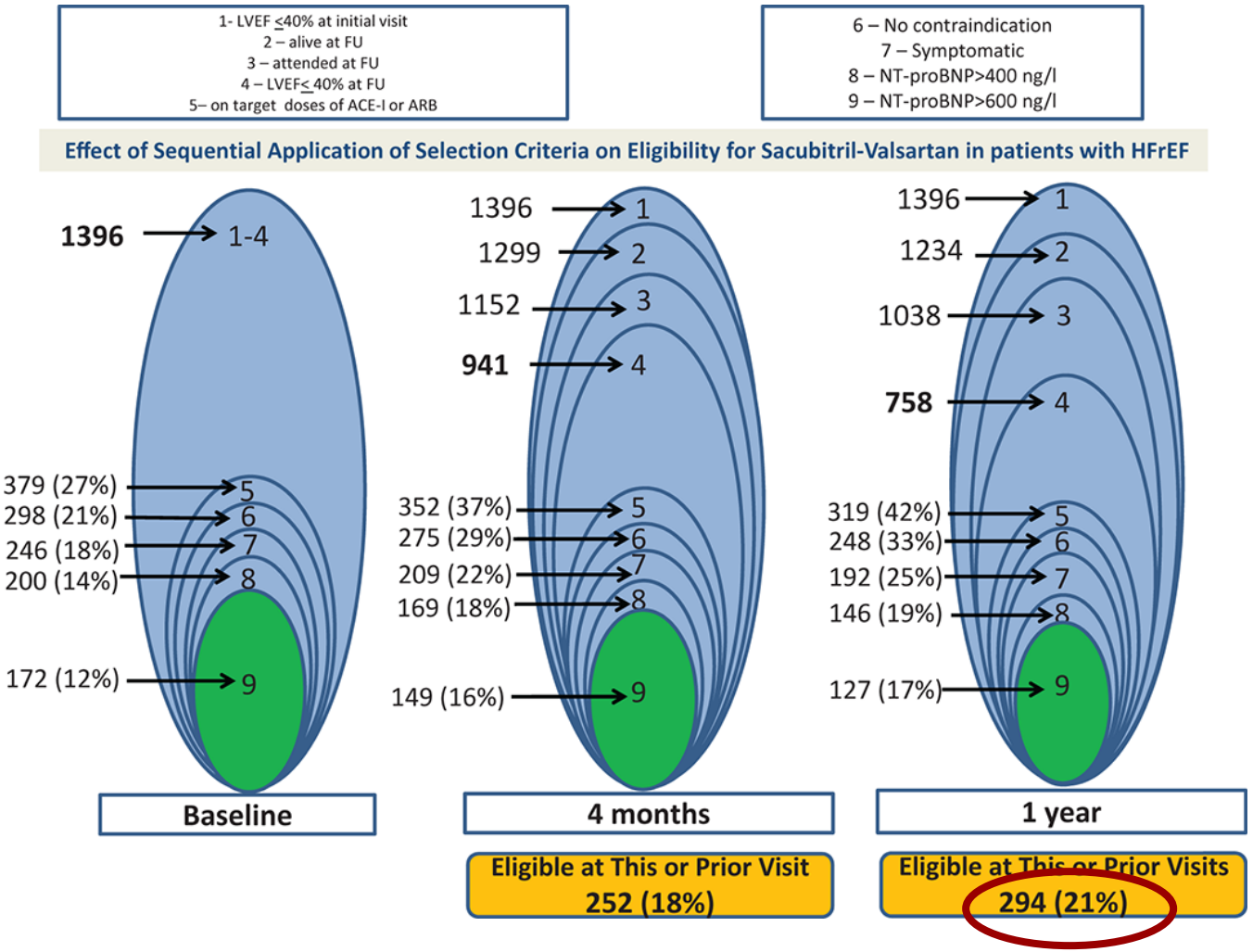
What proportion of patients with chronic heart failure are eligible for sacubitril–valsartan?

Pierpaolo Pellicori[1]*, Alessia Urbinati[1], Parin Shah[1], Alexandra MacNamara[1], Syed Kazmi[1], Riet Dierckx[1], Jufen Zhang[1], John G.F. Cleland[1,2], and Andrew L. Clark[1]

Methods and results Between 2001 and 2014, 6131 patients consecutively referred to a community HF clinic with suspected HF were assessed. The criteria required to enter the randomized phase of PARADIGM-HF, including symptoms, NT-proBNP, and current treatment with or without target doses of ACE inhibitors or ARBs, were applied to identify the proportion of patients eligible for sacubitril–valsartan. Recognizing the diversity of clinical opinion and guideline recommendations concerning this issue, entry criteria were applied singly and in combination. Of 1396 patients with reduced left ventricular ejection fraction (≤40%, HFrEF) and contemporary measurement of NT-proBNP, 379 were on target doses of an ACE inhibitor or ARB at their initial visit and, of these, 172 (45%) fulfilled the key entry criteria for the PARADIGM-HF trial. Lack of symptoms (32%) and NT-proBNP <600 ng/L (49%) were common reasons for failure to fulfil criteria. A further 122 patients became eligible during follow-up ($n = 294$, 21%). However, if background medication and doses were ignored, then 701 (50%) were eligible initially and a further 137 became eligible during follow-up.

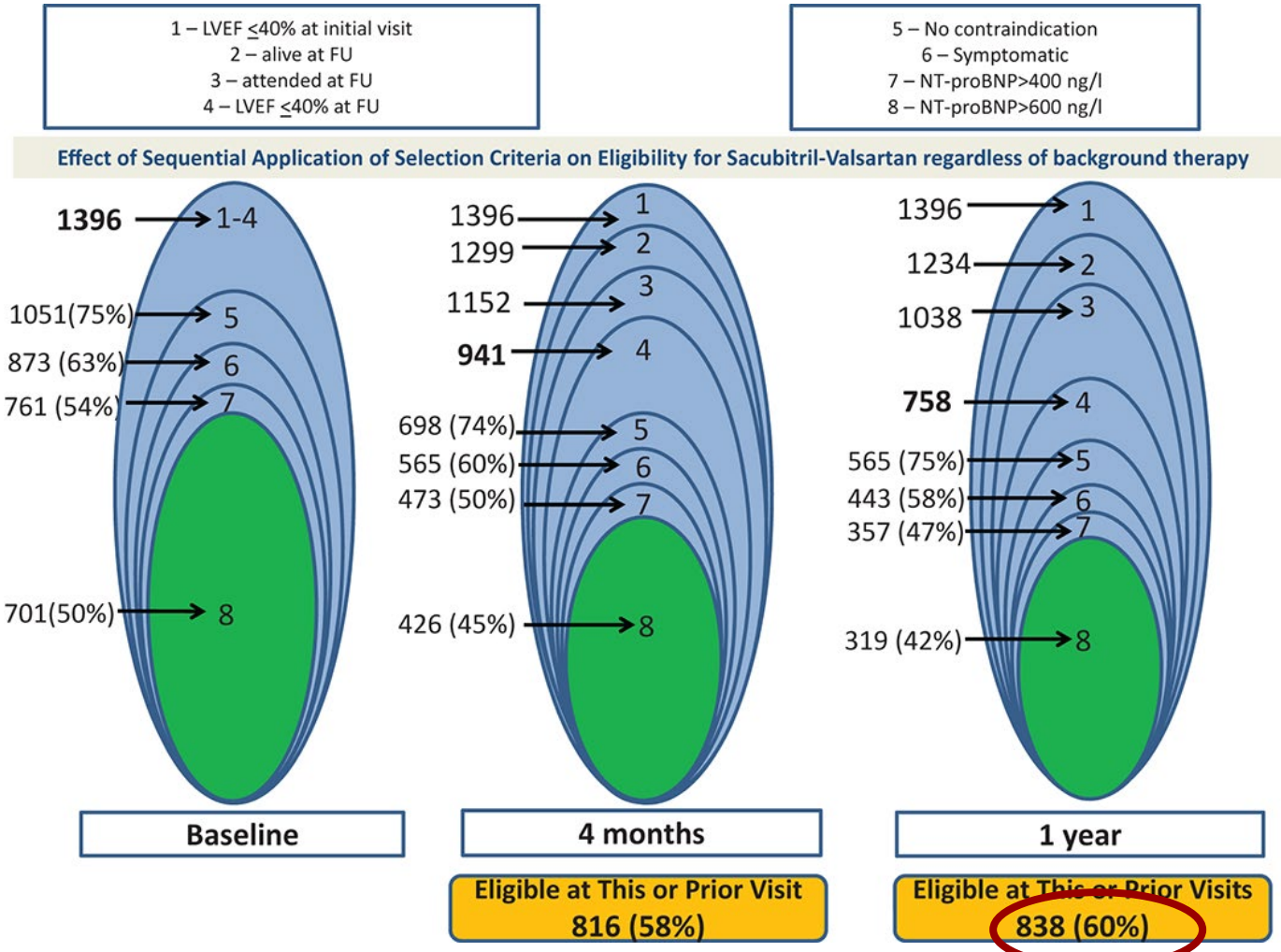
Conclusions Of patients with HFrEF referred to a clinic such as ours, only 21% fulfilled the PARADIGM-HF randomization criteria, on which the ESC Guidelines are based; this proportion rises to 60% if background medication is ignored.

What proportion of patients with chronic heart failure are eligible for sacubitril–valsartan?



Pellicori et a. Eur J Heart Fail 27 FEB 2017 DOI: 10.1002/ejhf.788

What proportion of patients with chronic heart failure are eligible for sacubitril–valsartan?
Selection regardless background therapy



Pellicori et a. Eur J Heart Fail 27 FEB 2017 DOI: 10.1002/ejhf.788

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.592

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Recommendations	Class [a]	Level [b]	Ref [c]
Angiotensin receptor neprilysin inhibitor			
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B	162

[d]Patient should have elevated natriuretic peptides (plasma BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalization within the last 12 months, plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL) and able to tolerate enalapril 10 mg *b.i.d.*

Ponikowski et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

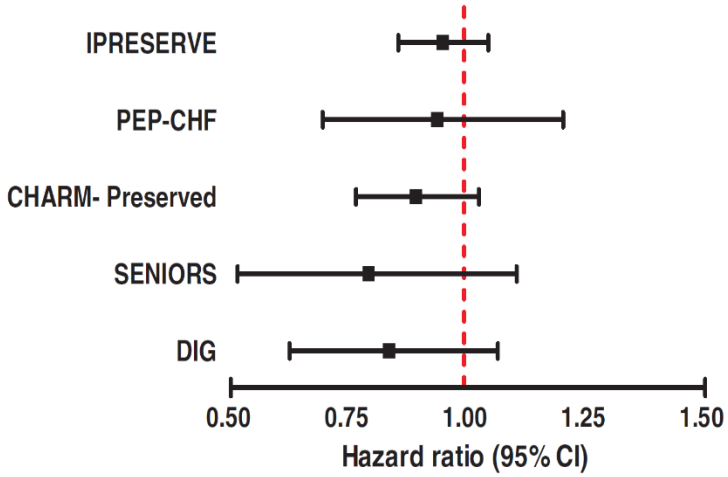
Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL.



Linee Guida ESC 2016

New drugs for treatment of chronic heart failure

Drug	Status
HFrEF	
LCZ696 / Sacubitril/Valsartan	Approved and indicated
Finerenone	Not now studied in HF
Potassium binders	Under approval
Vericiguat	Phase 3 (VICTORIA)
Omecamtiv mecarbil	Maybe phase 3
Neuregulin	Phase 3
HFpEF	
LCZ696 / Sacubitril/Valsartan	Phase 3 (PARAGON)
Sodium nitrite	Mechanistic studies
Vericiguat	Phase 3 (VITALITY)
Others	
STG-2 Inhibitors	Phase 3 in HF alone
Ferric carboxymalthose	Phase 3
Rivaroxaban	Phase 3