CHRONIC HEART FAILURE: ADVANCED MANAGEMENT TO PREVENT READMISSION

Dr. Nani Hersunarti, SpJP (K)

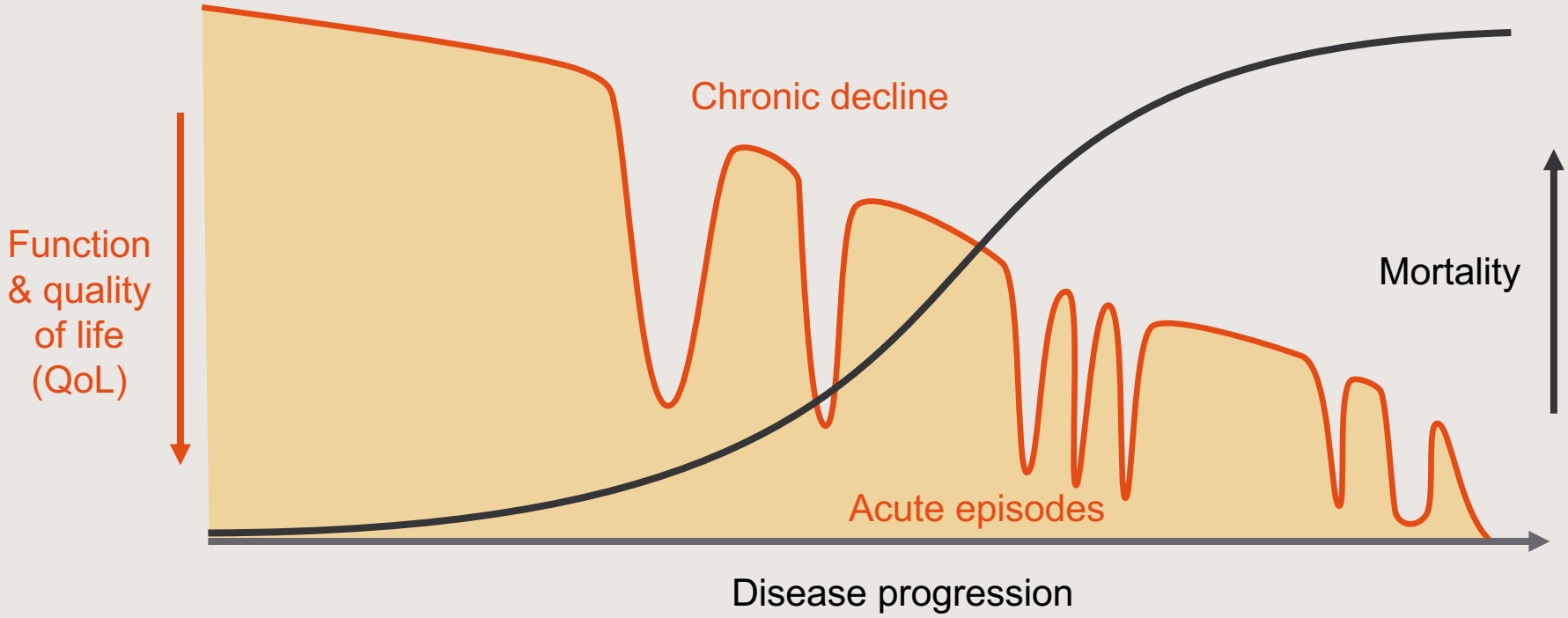
Epidemiology, Etiology and Natural History of Heart Failure

- **1–2% of the adult population** in developed countries, rising to **≥10% among people > 70 years of age**
- Among people **> 65 years of age** presenting to primary care with breathlessness on exertion, **one in six will have unrecognized HF (mainly HFpEF)**

A Progressive Condition with High Mortality

Clinical Manifestations

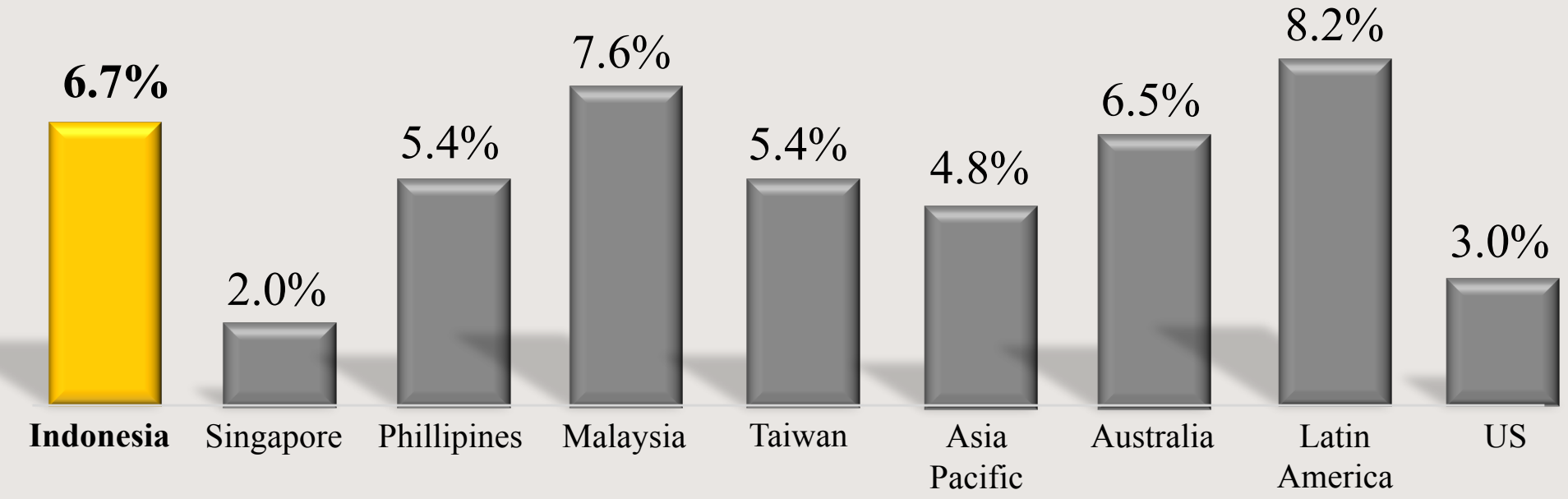
- **Increasing frequency of acute events** with disease progression **leads to high rates of hospitalization and increased risk of mortality**
- With **each acute event,** myocardial injury may contribute to **progressive LV dysfunction**



LV: left ventricular

Gheorghiade et al. Am J Cardiol 2005;96:11G–17G; Gheorghiade & Pang. J Am Coll Cardiol 2009;53:557–73

Heart Failure Patients in Indonesia has Relatively High Rate of In-Hospital Mortality



1. Siswanto et al, 2010. Heart Failure in NCVC Jakarta and 5 hospitals in Indonesia. CVD Prevention and Control, 5, 35– 38
2. Ponikowski et al, 2014. Heart failure: preventing disease and death worldwide. ESC Heart Failure, 1: 4–25

Clinical Inertia on Heart Failure Management in Indonesia

Unmet Needs of Heart Failure Management

Miss diagnosis/ Underdiagnosis

Sub optimal pharmacological treatment

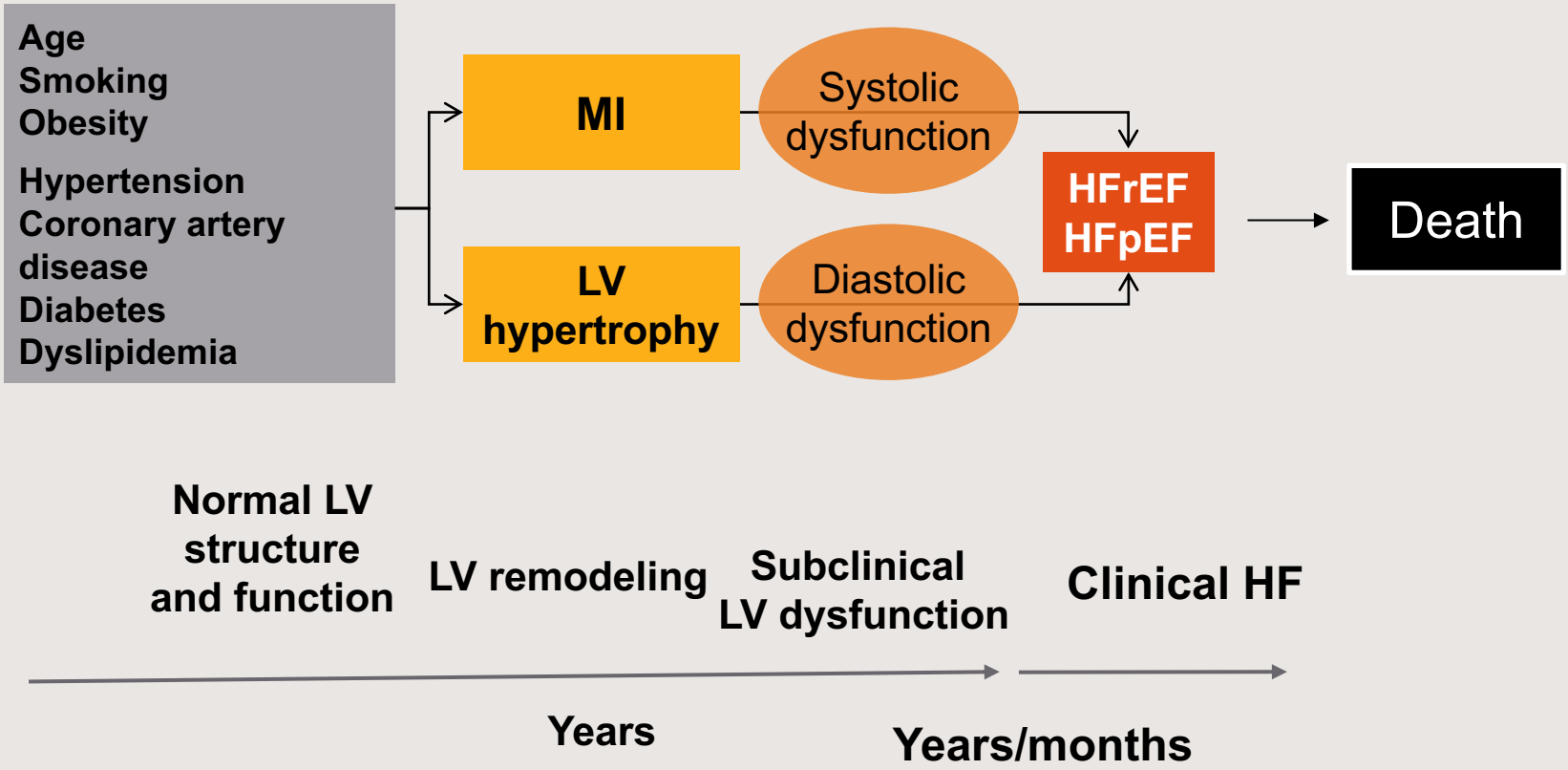
Physician and patients low adherence

Economic and social high burden

Poor Prognosis

Different Co-morbidities and Pathophysiological Processes can Lead to Different Types of Heart Failure

A range of risk factors and co-morbidities contribute to the development of HF[1]



‡ Patients with an LV ejection fraction of 35–50% represent a 'gray area' and may have primarily mild systolic dysfunction2
HF=heart failure; LV=left ventricular; LVEF=left ventricular ejection fraction;MI=myocardial infarction

1. Krum, Gilbert. Lancet 2003;362:147–58;

Cardiac Dysfunction Triggers The Activation of Three Compensatory Neurohormonal Systems

Cardiac structure/function abnormality

↓

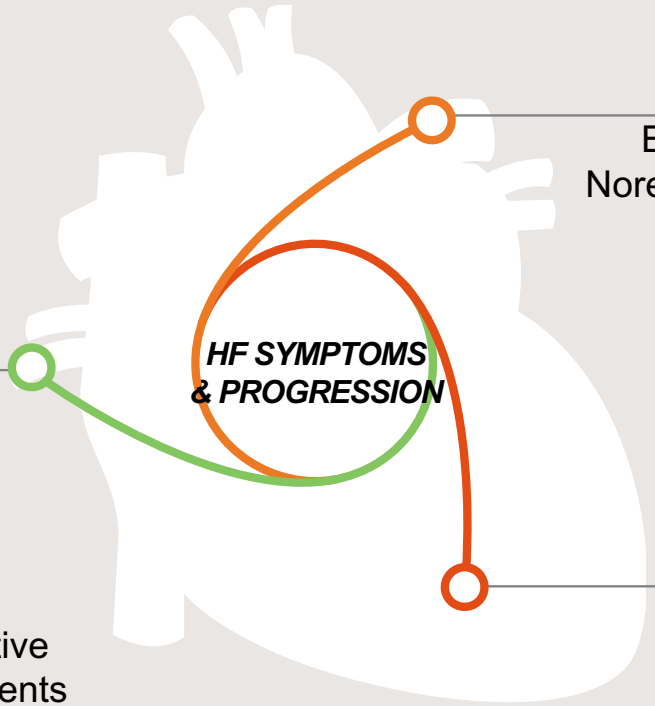
Activation of **compensatory mechanisms** to maintain cardiac output and organ perfusion[1]

SNS	*RAAS*	*NP system*
Activated in response to reduced cardiac output[1]		Release of NPs in response to cardiac stress[2]
Short-term effects are beneficial in early HF[1]		Opposes the actions of the RAAS[2] and SNS[4,5]
Long-term activation exerts unfavourable effects[1,3]		

NP=natriuretic peptide; RAAS=renin angiotensin aldosterone system;SNS=sympathetic nervous system

1. Francis et al. Ann Intern Med 1984;101:370–7; 2. Clerico et al. Am J Physiol Heart Circ Physiol 2011;301:H12–H20;
3. Von Lueder et al. Circ Heart Fail 2013;6:594–605 4. Luchner & Schunkert. Cardiovasc Res 2004;63:443–9;
5. Thysgesen et al. Eur Heart J 2012;33:2001–6

Three Core Neurohormonal System in Heart Failure



NP system

NPRs ← NPs

Vasodilation

- ↓ Blood pressure
- ↓ Sympathetic tone
- ↑ Natriuresis/diuresis
- ↓ Vasopressin
- ↓ Aldosterone
- ↓ Fibrosis
- ↓ Hypertrophy

Neprilysin → Inactive fragments

SNS

Epinephrine, Norepinephrine → α_1, β_1, β_2 receptors

Vasoconstriction

- RAAS activity ↑
- Vasopressin ↑
- Heart rate ↑
- Contractility ↑

RAAS

Ang II → AT_1R

Vasoconstriction

- Blood pressure ↑
- Sympathetic tone ↑
- Aldosterone ↑
- Hypertrophy ↑
- Fibrosis ↑
- Sodium and water retention ↑

ANG=angiotensin; AT1R=angiotensin type 1 receptor; NP=natriuretic peptide; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Kemp & Conte. Cardiovascular Pathology 2012;365–371; Schrier et al. Kidney Int 2000;57:1418–25; Schrier & Abraham N Engl J Med 2009;341:577–85; Boerrigter, Burnett. Expert Opin Invest Drugs 2004;13:643–52; Ferro et al. Circulation 1998;97:2323–30; Brewster et al. Am J Med Sci 2003;326:15–24

Pharmacological Treatment

Do we need new therapy?

Mortality rates are still **high**-aprox 50% at 5 years [1-5]

There is a **new therapeutic option** targeting the natriuretic peptide system

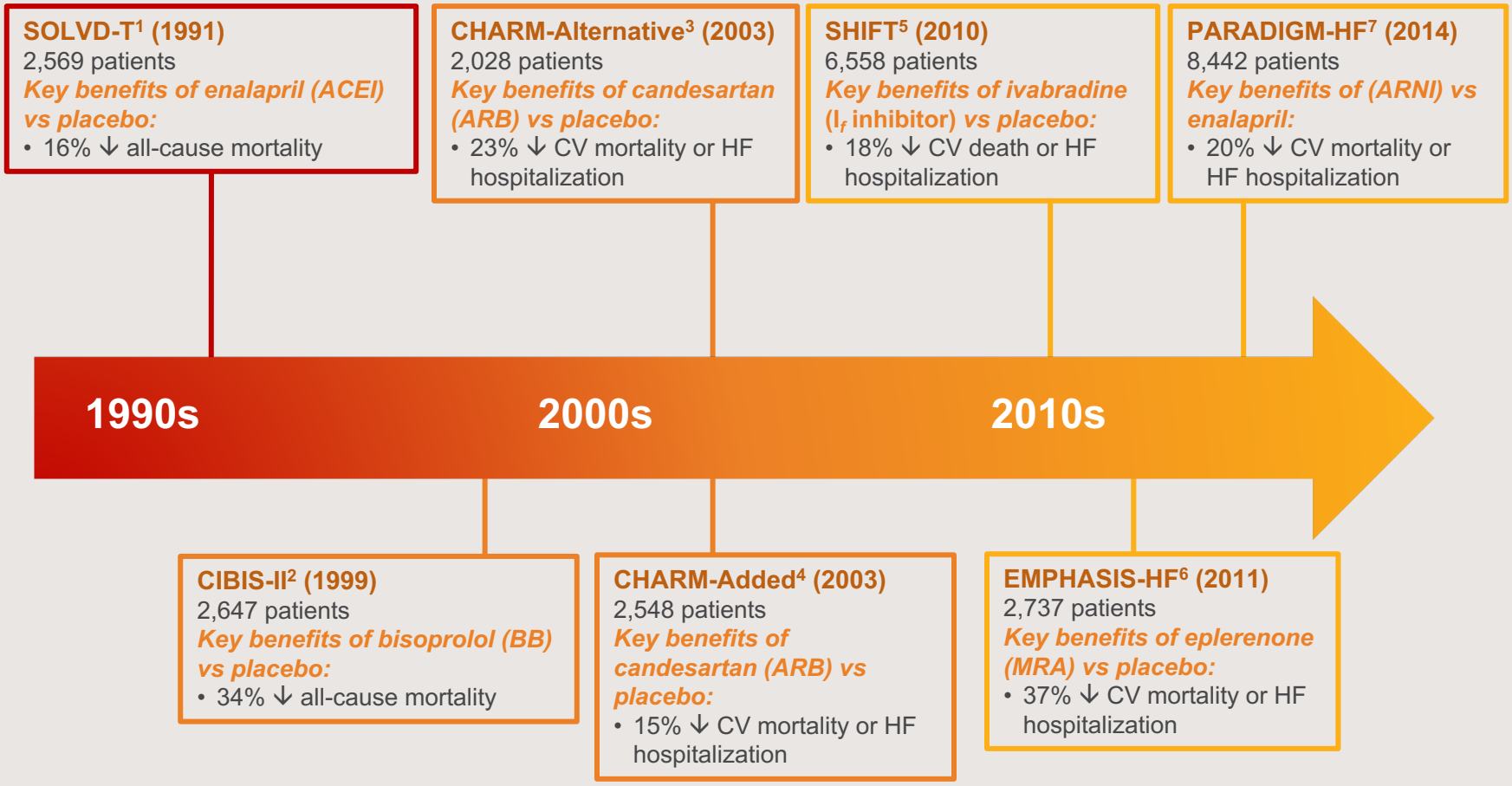
PARADIGM-HF prospectively **compared ARNI and ACEI** to determine impact on global mortality and morbidity in HF [7]

PARAGON-HF is an **ongoing study** comparing LCZ696 with valsartan in patient with HF-PEF [8]

ARNI, angiotensin receptor–neprilysin inhibitor; ACEI, angiotensin-converting-enzyme inhibitor.

1. Levy D, et al. N Engl J Med. 2002;347:1397-402. 2. Roger VL, et al. JAMA. 2004;292:344-50. 3. Hobbs FD, et al. Eur Heart J. 2007;28:1128-34. 4. Henkel DM, et a. Circ Heart Fail. 2008;1:91-7. 5. Zarrinkoub R, et al. Eur J Heart Fail. 2013;15:995-1002. 6. McMurray JJ, et al. Eur Heart J. 2012;33:1787-847. 7. McMurray JJ, et al. N Engl J Med. 2014;371:993-1004. 8. NCT01920711. Available from: https://clinicaltrials.gov/ct2/show/NCT01920711. Accessed November 2015.

Landmark Trials in Patients with HFrEF

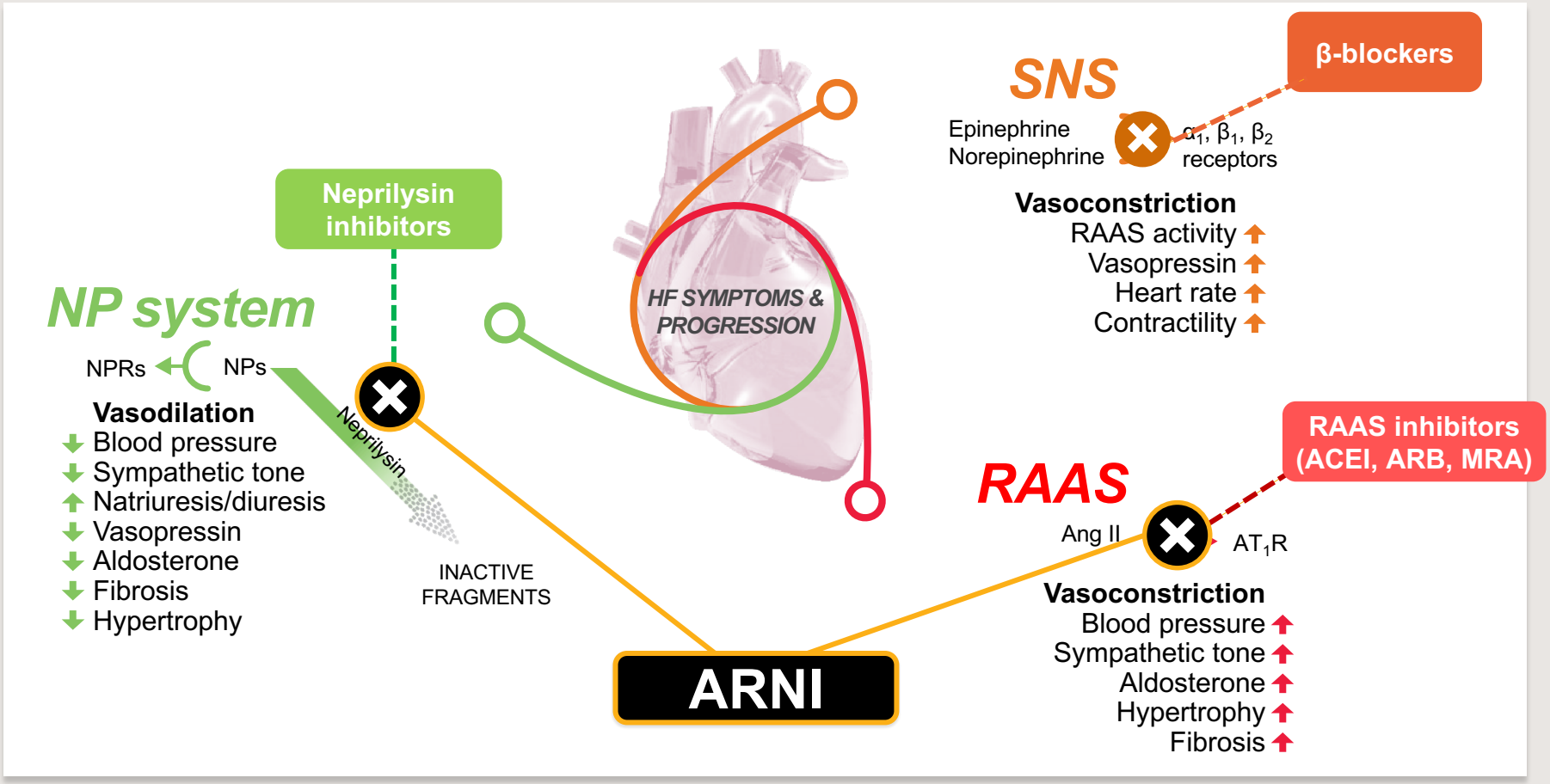


Percentages are relative risk reductions vs comparator

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor neprilysin inhibitor; BB=beta blocker; CV=cardiovascular; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; MRA=mineralocorticoid receptor antagonist. See notes for definitions of study names

1. SOLVD Investigators. N Engl J Med 1991;325:293–302
2. CIBIS-II Investigators. Lancet 1999;353:9–13; 3. Granger et al. Lancet 2003;362:772−6
4. McMurray et al. Lancet 2003;362:767–771; 5. Swedberg et al. Lancet 2010;376:875–85
6. Zannad et al. N Engl J Med 2011;364:11–21; 7. McMurray et al. N Engl J Med 2014;371:993–1004

Evolution of Pharmacologic Approaches in HF: ARNI as a New Alternative to an ACEI or ARBs in Patients with HFrEF[1]



- ARNI: enhancement of natriuretic and other vasoactive peptides, with simultaneous RAAS suppression

ACEI=angiotensin-converting enzyme inhibitor; Ang=angiotensin; ARB=angiotensin receptor blocker; AT_1R=angiotensin II type 1 receptor; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; MRA=mineralocorticoid receptor antagonist; NP=natriuretic peptide; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

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

Figure references: Levin et al. N Engl J Med 1998;339:321–8 Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42 Kemp & Conte. Cardiovascular Pathology 2012;365–71 Schrier & Abraham. N Engl J Med 2009;341:577–85

PARADIGM-HF

Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure

ARNI Clinical Study :

PARADIGM-HF

Primary objective : to evaluate the effect of LCZ696 200 mg BID compared with enalapril 10 mg BID, in addition to conventional HFrEF treatment, in delaying **time to first occurrence** of either **CV death** or **HF hospitalization**[1]

Chronic HF NYHA FC II–IV with LVEF ≤40%
SBP ≥ 100 mmHg at screening

Randomization
n=8442

Single-blind active run-in period

Enalapril 10 mg BID*
LCZ696 100 mg BID†
LCZ696 200 mg BID‡

Double-blind Treatment period

LCZ696 200 mg BID‡
Enalapril 10 mg BID§

2 Weeks | **1–2 Weeks** | **2–4 Weeks** | **Median of 27 months' follow-up**

On top of standard HFrEF therapy (excluding ACEIs and ARBs)

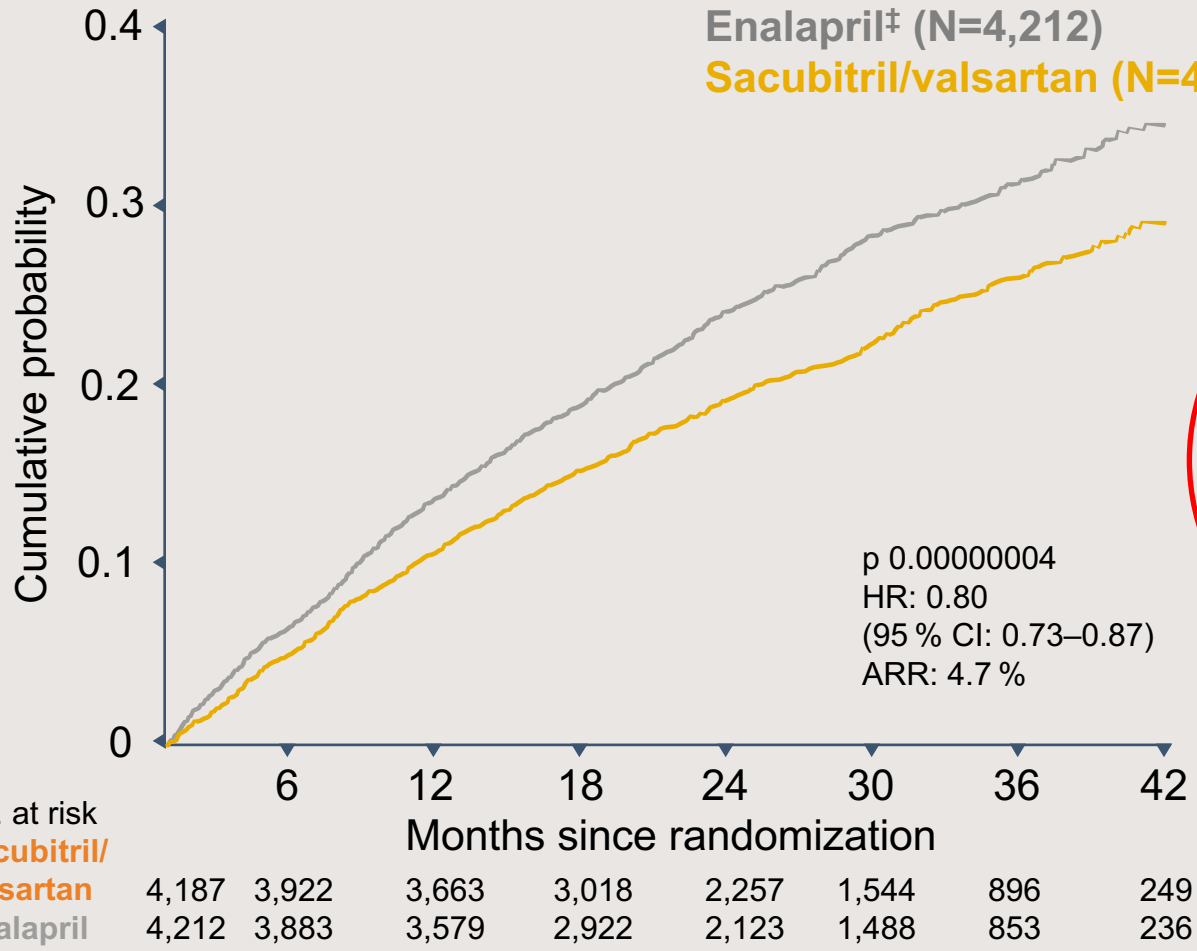
*Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; †200 mg TDD; ‡400 mg TDD; §20 mg TDD.

McMurray et al. Eur J Heart Fail. 2013;15:1062–73; McMurray et al. Eur J Heart Fail. 2014;16:817–25;
McMurray, et al. N Engl J Med 2014; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.

Disclaimer : LCZ696 has not yet been marketed in Indonesia

PARADIGM-HF
Primary and Secondary Outcomes

Primary Outcome
Sacubitril/valsartan Significantly Reduced
Death from CV Causes or First Hospitalization for HF*



NNT 21§

20%
RELATIVE RISK REDUCTION OF PRIMARY ENDPOINT

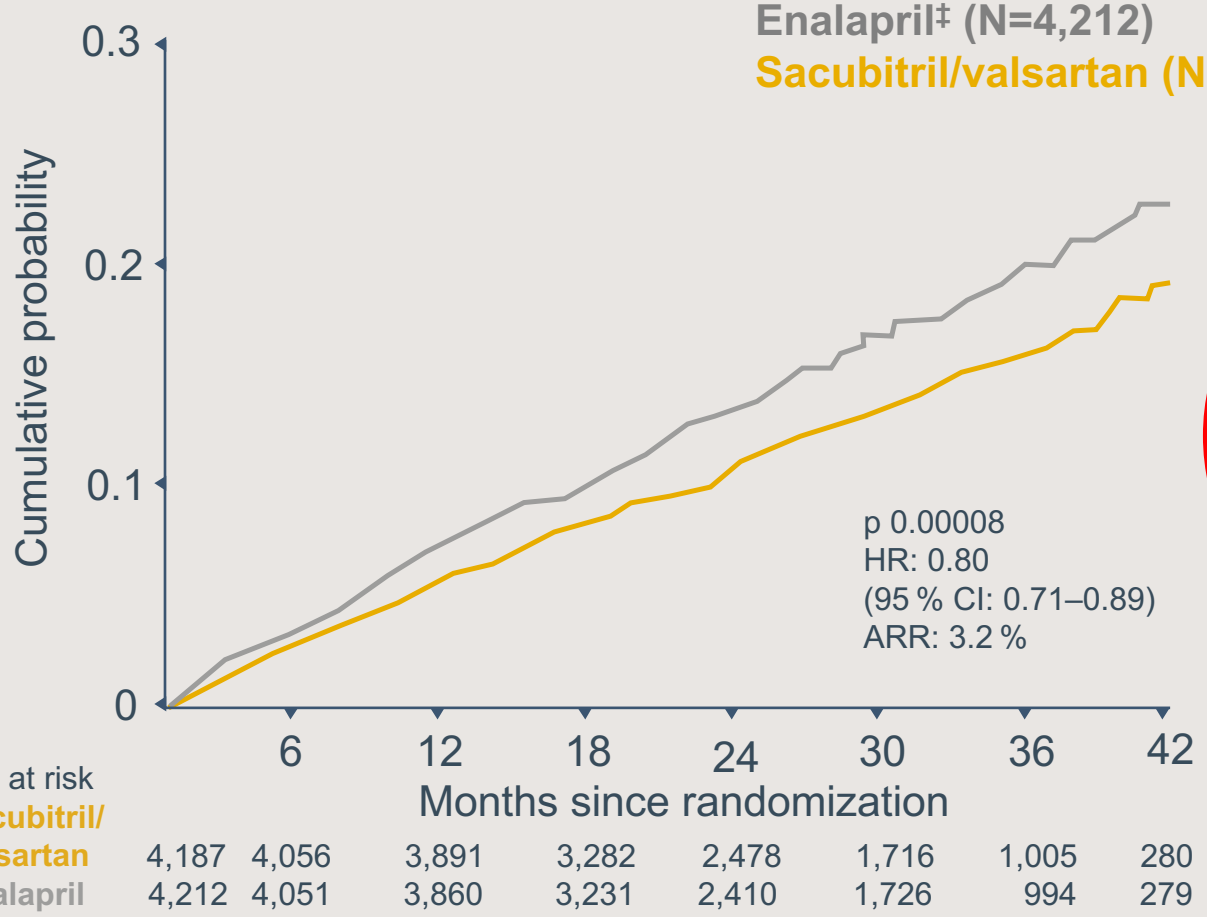
No. at risk								
Sacubitril/valsartan	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

*Compared with enalapril, as assessed via time until cardiovascular death or first hospitalization for HF.[1] ‡Enalapril 10 mg 2x daily as comparator vs sacubitril/valsartan 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy). §27 months since randomization (median)

ACE=angiotensin-converting enzyme; ARR=absolute risk reduction; CI=confidence interval; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; HR=hazard ratio; NNT=number needed to treat

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

Primary Outcome
Sacubitril/valsartan Significantly Reduced
CV Mortality*

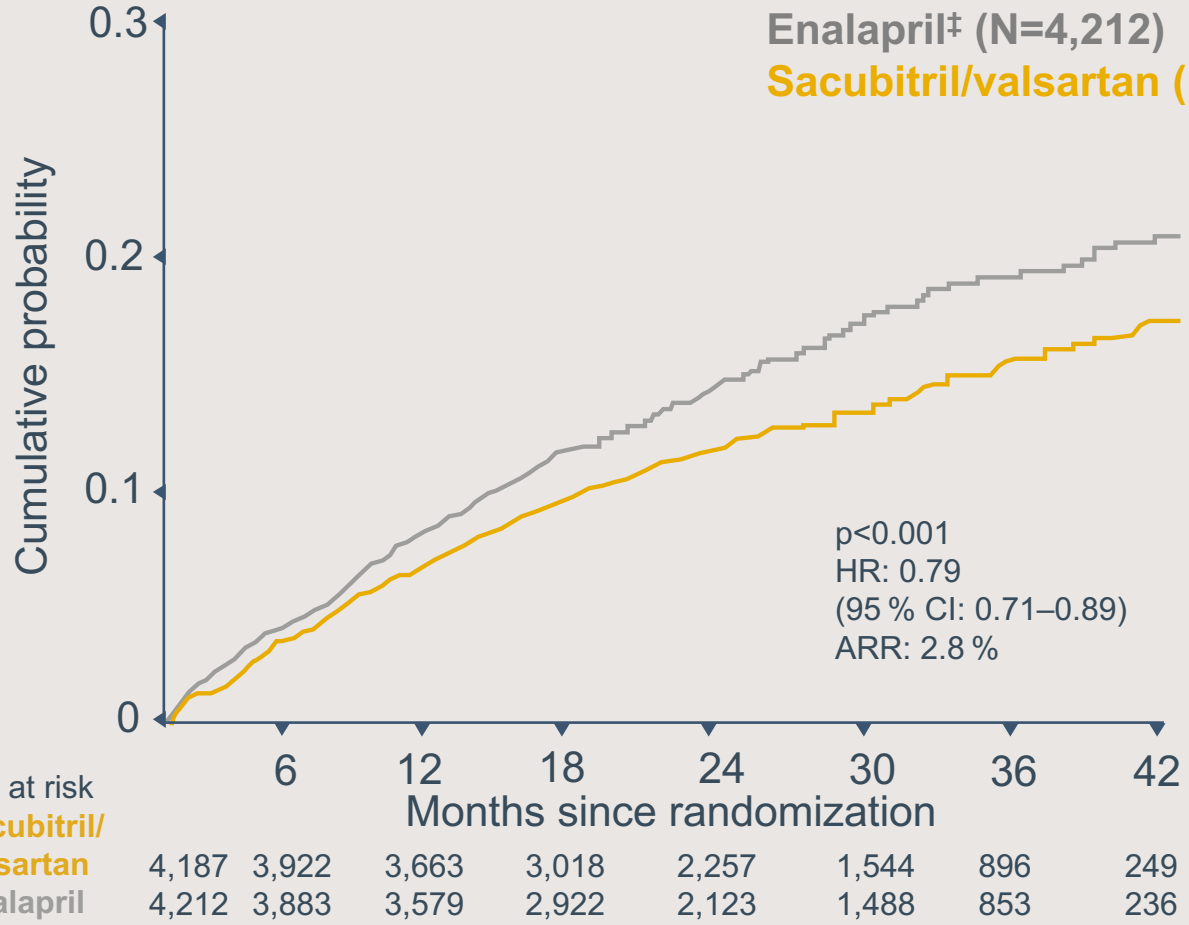


NNT 32§

20%
RELATIVE RISK REDUCTION OF CARDIOVASCULAR MORTALITY

*Time to cardiovascular death. ‡Enalapril 10 mg 2x daily as comparator vs sacubitril/valsartan 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy). §27 months since randomization (median)
ACE=angiotensin-converting enzyme; ARR=absolute risk reduction; CI=confidence interval; CV=cardiovascular; HR=hazard ratio
McMurray et al. N Engl J Med 2014;371:993–1004

Primary Outcome
Sacubitril/valsartan Significantly Reduces the Risk of First HF Hospitalization, Keeping HFrEF Patients Out of The Hospital*



No. at risk								
Sacubitril/valsartan	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

NNT 32§

21%

RELATIVE RISK REDUCTION OF FIRST HOSPITALIZATION FOR HF

*Compared with enalapril, as assessed via time to first hospitalization for HF (single component of primary endpoint). ‡Enalapril 10 mg 2x daily as comparator vs sacubitril/valsartan 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy). §27 months since randomization (median)

ACE=angiotensin-converting enzyme; ARR=absolute risk reduction; CI=confidence interval; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; HR=hazard ratio; NNT=number needed to treat

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

Primary Outcomes – Summary

Outcome, n %	LCZ696 (n=4187)	Enalapril (n=4212)	Hazard ratio* (95% CI)	p-value‡
Primary composite outcome				
Death from CV causes or first hospitalization for worsening of HF	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from CV causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening of HF	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001

*Calculated with the use of stratified cox proportional-hazard models
‡Two-sided p-values calculated by means of a stratified log-rank test without adjustment for multiple comparisons

Disclaimer : LCZ696 has not yet been marketed in Indonesia

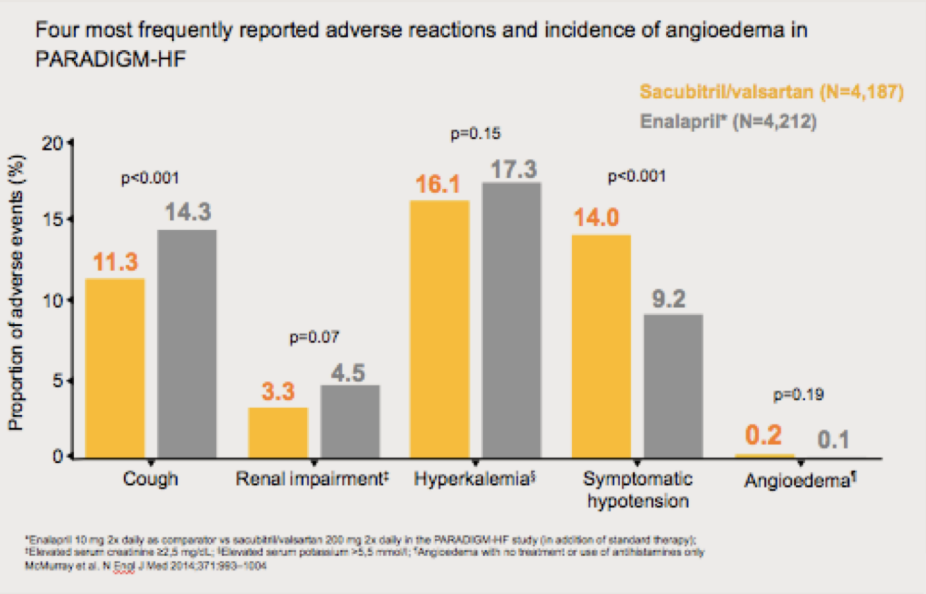
McMurray, et al. N Engl J Med 2014; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.

Secondary Outcomes

Outcome, n %	Sacubitril/ valsartan (n=4,187)	Enalapril (n=4,212)	Hazard ratio* (95% CI)	p value‡
Death from any cause, n (%)	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	< 0.001
Change in KCCQ clinical summary score§ at 8 months, mean ± SD	–2.99 ± 0.36	–4.63 ± 0.36	1.64 (0.63–2.65)	< 0.001
New onset atrial fibrillation¶, n (%)	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function#, n (%)	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

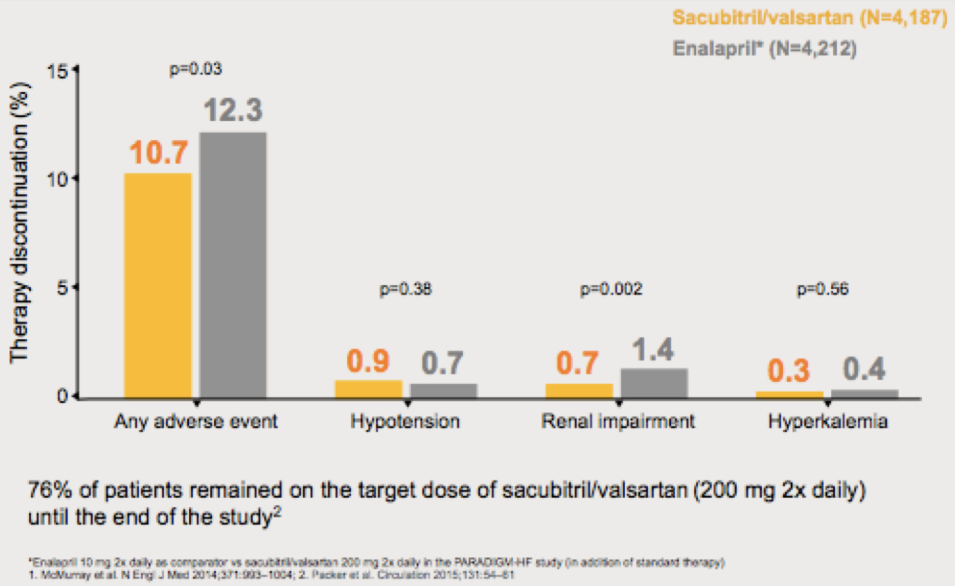
*Calculated with the use of stratified cox proportional-hazard models; ‡Two-sided p values calculated by means of a stratified log-rank test without adjustment for multiple comparisons; §KCCQ scores range from 0 to 100 – higher scores indicate fewer symptoms and physical limitations associated with HF; ¶2,670 patients in the sacubitril/valsartan and 2,638 in the enalapril group who did not have atrial fibrillation at randomization were evaluated; #Defined as: (a) ≥50% decline in eGFR from randomization; (b) >30 mL/min/1.73 m^2 decline in eGFR from randomization or to a value of <60 mL/min/1.73 m^2, or (c) progression to end-stage renal disease.
CI=confidence interval; eGFR=estimated glomerular filtration rate; HF=heart failure; KCCQ=Kansas City Cardiomyopathy Questionnaire; SD=standard deviation
McMurray et al. N Engl J Med 2014;371:993–1004

Additional Outcomes



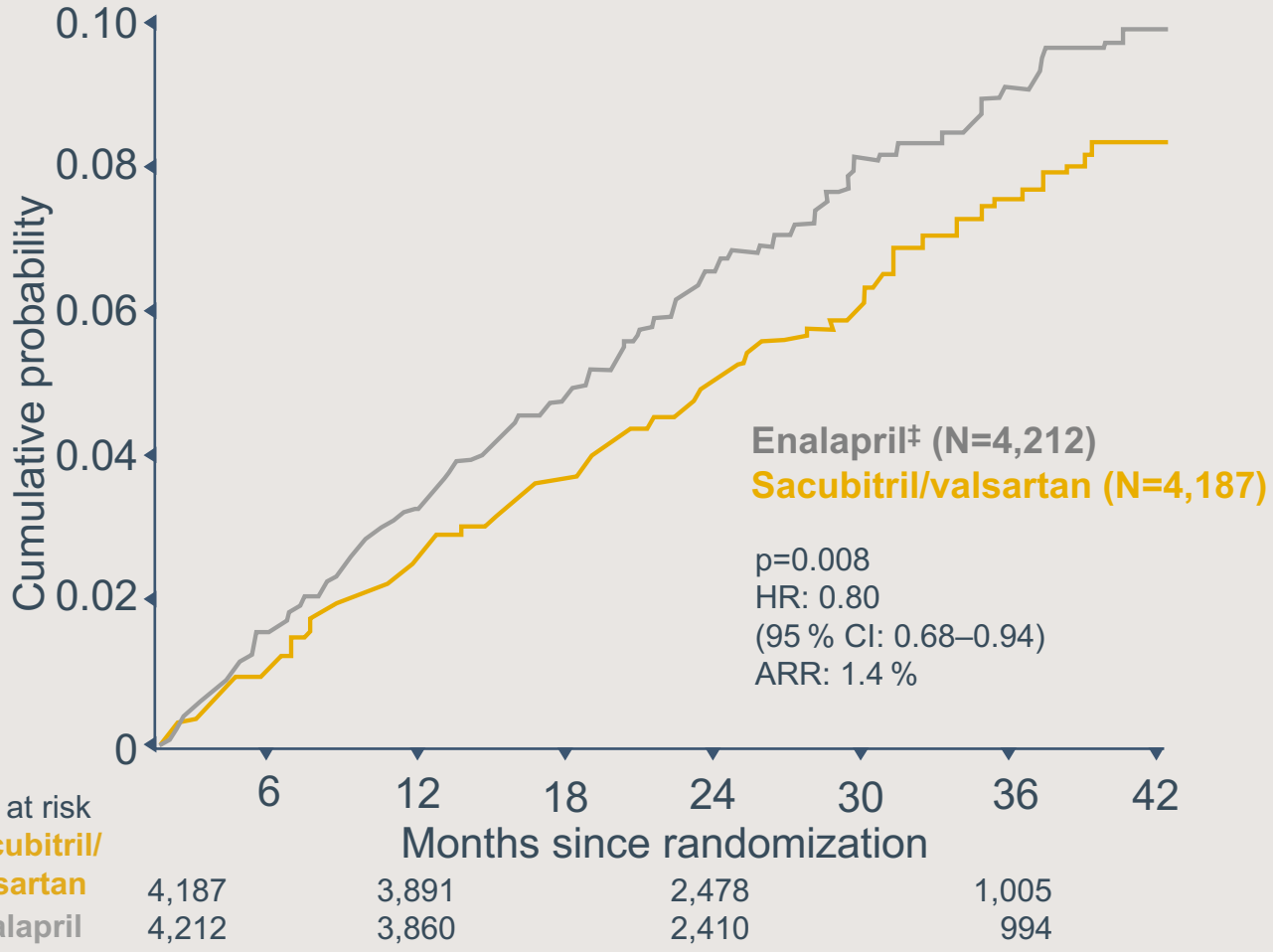
Sacubitril/valsartan has a safety and tolerability profile comparable to that of enalapril

Sacubitril/valsartan had fewer adverse events leading to permanent study drug discontinuation[1]



PARADIGM-HF
Additional Mortality & Morbidity Data

Sacubitril/valsartan Significantly Reduced the Risk of Sudden Death[1]



NNT 71§

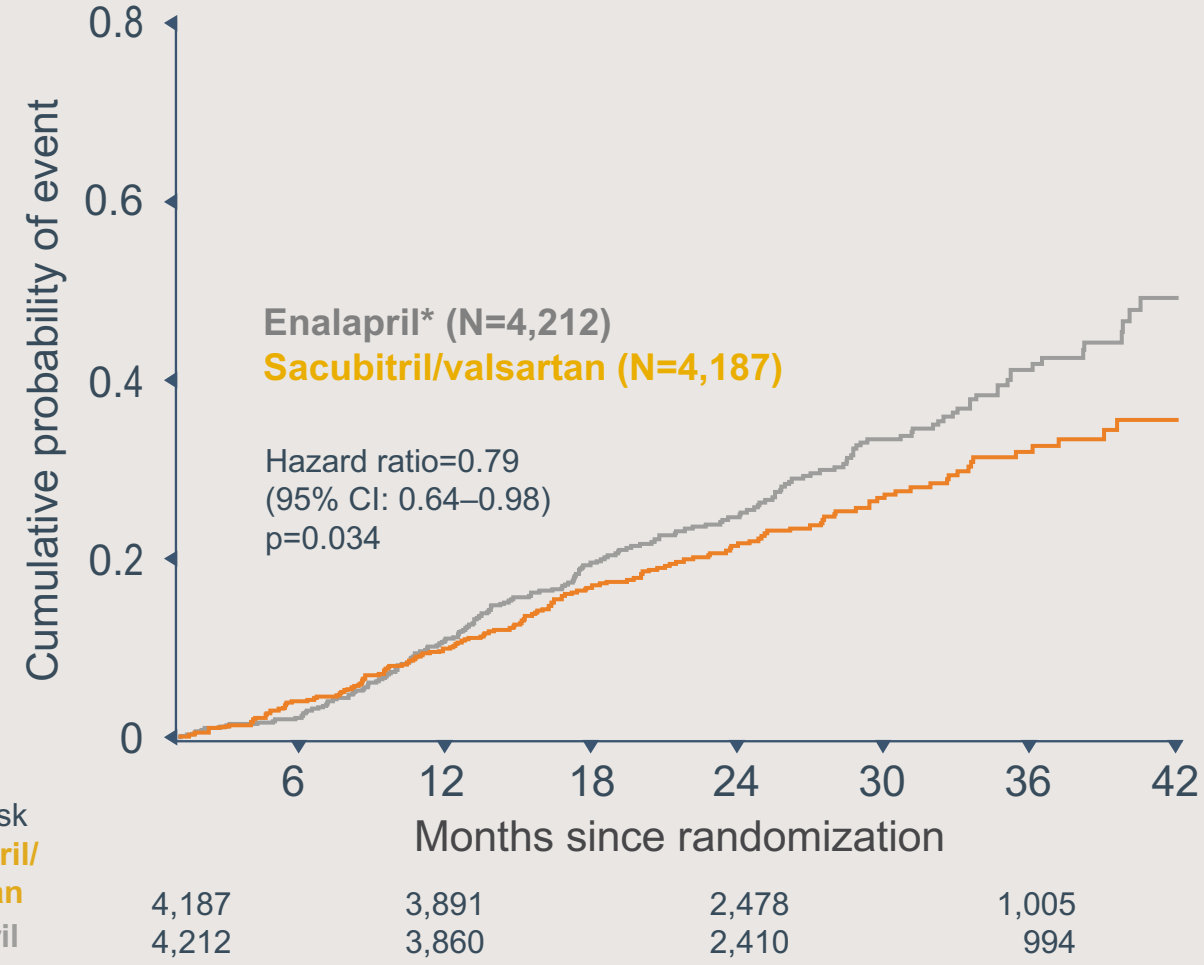
20%

RELATIVE RISK REDUCTION OF SUDDEN DEATH

*Enalapril 10 mg 2x daily as comparator vs sacubitril/valsartan 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy). §27 months since randomization (median)
ARR=absolute risk reduction; CI=confidence interval; HR=Hazard Ratio; NNT=number needed to treat

1. Desai et al. Eur Heart J 2015;36:1990–7

Death Due to Worsening of Heart Failure was Significantly Reduced by Sacubitril/valsartan Treatment, Compared with Enalapril



20%

RELATIVE RISK REDUCTION
Death due to worsening of heart failure

*Enalapril 10 mg 2x daily as comparator vs sacubitril/valsartan 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy). CI=confidence interval

Desai et al. Eur Heart J 2015;36:1990–7

Sacubitril/valsartan Reduced the Frequency and Severity of Hospitalizations Compared to Enalapril*

30%

FEWER VISITS
TO THE EMERGENCY UNIT FOR HEART FAILURE

p=0.017

18%

FEWER STAYS
IN INTENSIVE CARE UNITS

p=0.005

12%

LOWER RISK
OF ALL-CAUSE HOSPITALIZATION

p<0.001

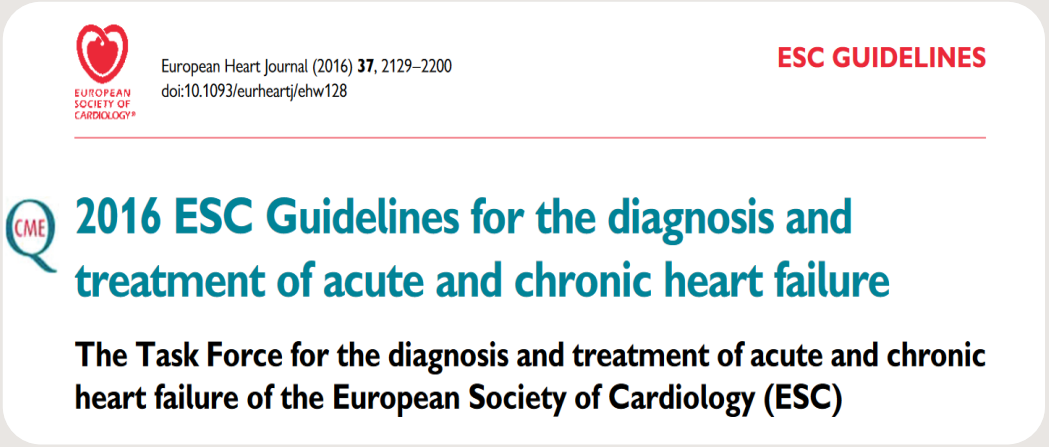
*Enalapril 10 mg 2x daily as comparator vs sacubitril/valsartan 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy).
Packer et al. Circulation 2015;131:54–61

IVABRADINE

Its effect is to **slow the heart rate** in patients in **sinus rhythm**

SHIFT Trial : Ivabradine reduced mortality or hospitalization by 18% in NYHA II – IV HF patients with **heart rate ≥ 70 bpm after given optimal recommended therapy** (including diuretic, digoxin, ACE-I, ARB, beta-blocker, MRA)

WHAT DO THE GUIDELINES SAY?



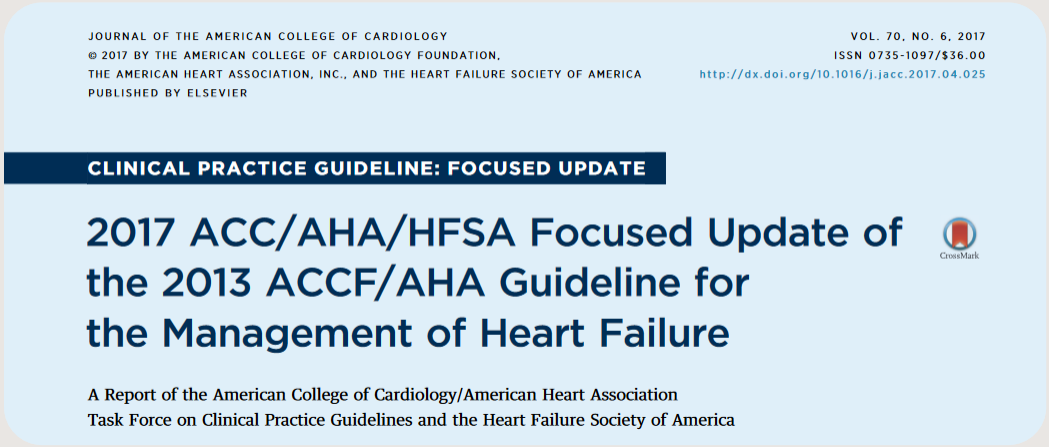
European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

CME

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)



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION,
THE AMERICAN HEART ASSOCIATION, INC., AND THE HEART FAILURE SOCIETY OF AMERICA
PUBLISHED BY ELSEVIER

VOL. 70, NO. 6, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.04.025

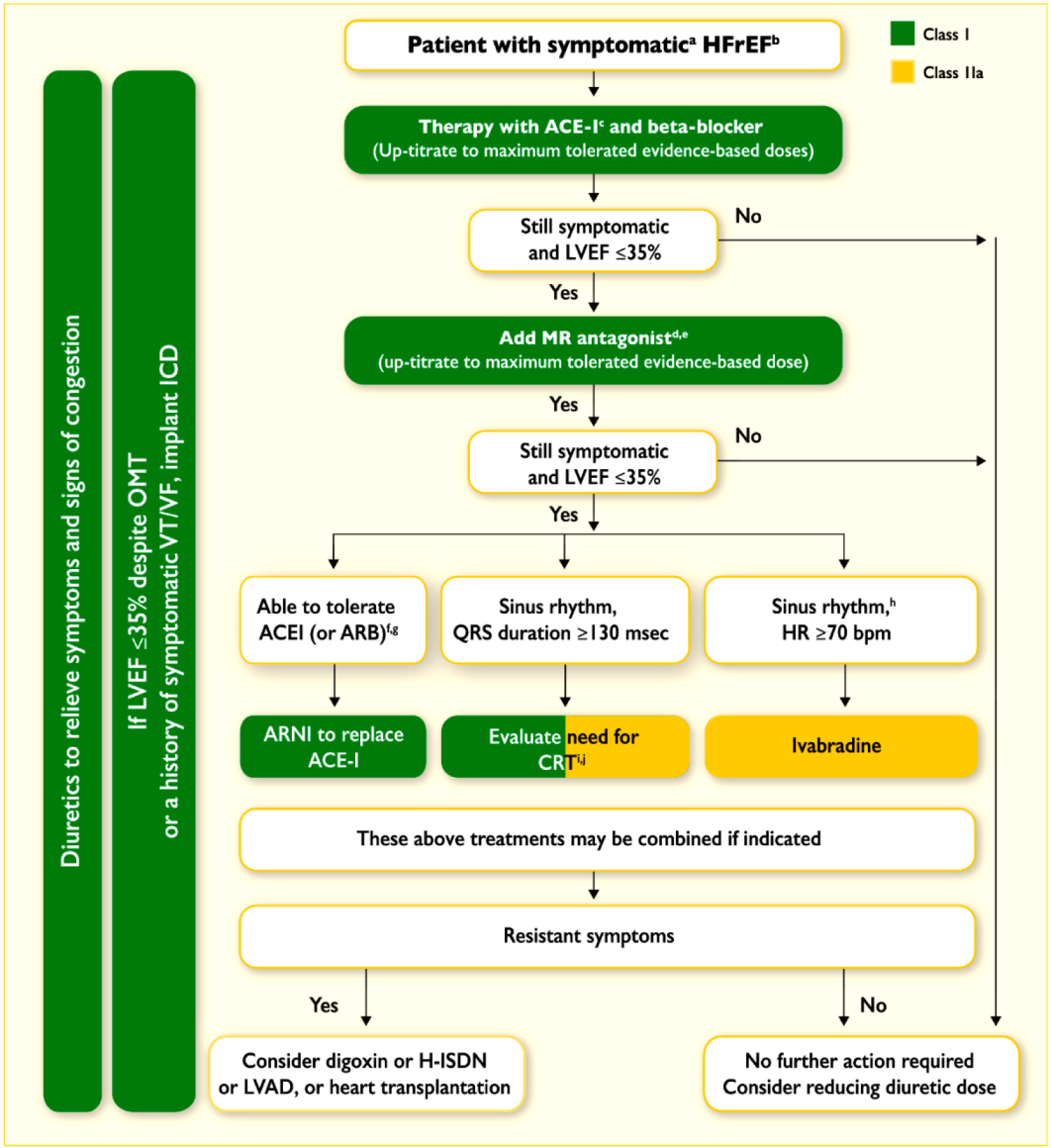
CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association
Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

2016 ESC Guideline

Therapeutic Algorithm for Symptomatic HFrEF

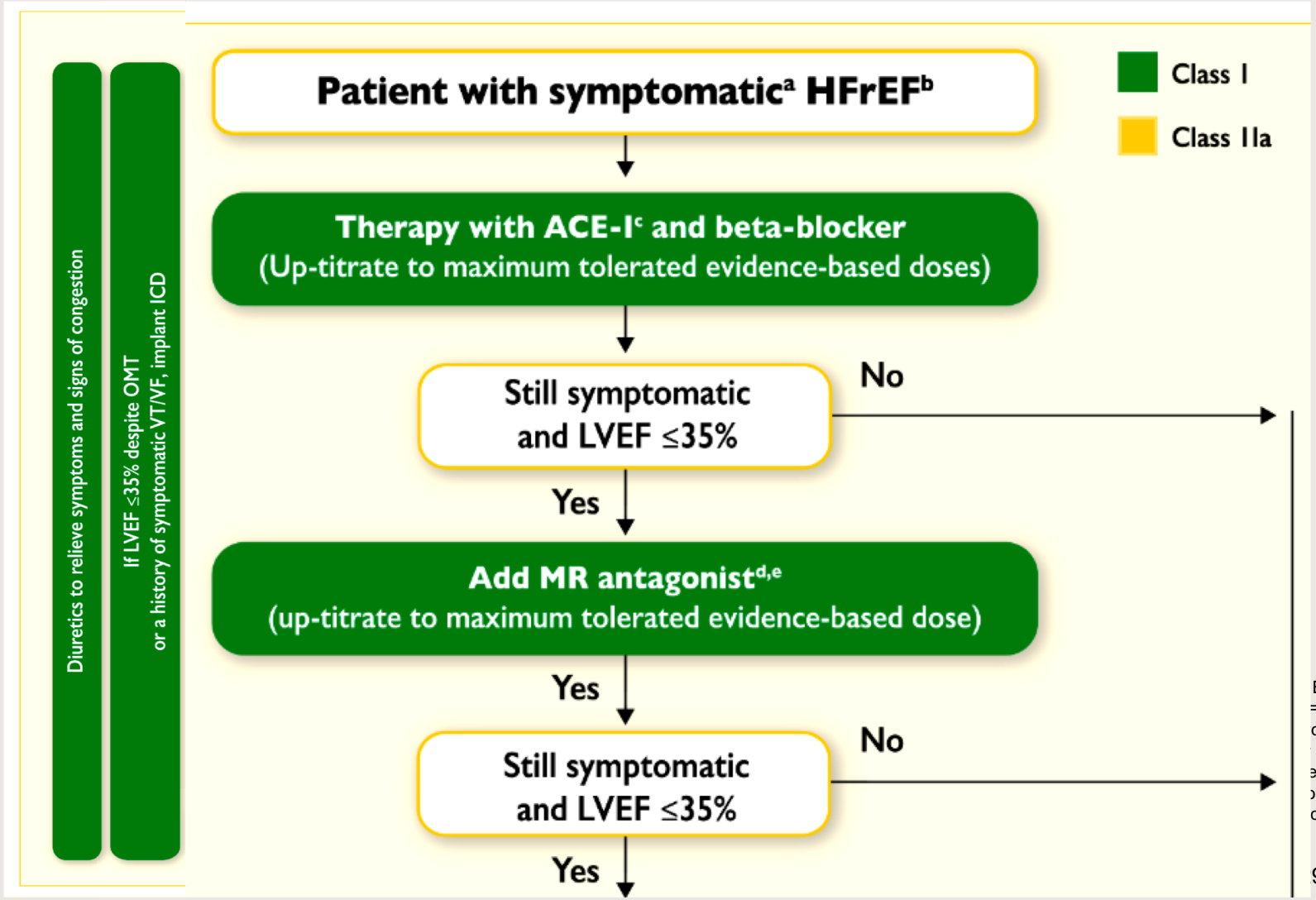


ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR = mineralocorticoid receptor; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Assoc0iation; OMT = optimal medical therapy; VF = ventricular fibrillation; VT = ventricular tachycardia.

. Ponikowski et al. Eur Heart J 2016; 37(27): 2129-2200

2016 ESC Guideline

Therapeutic Algorithm for Symptomatic HFrEF

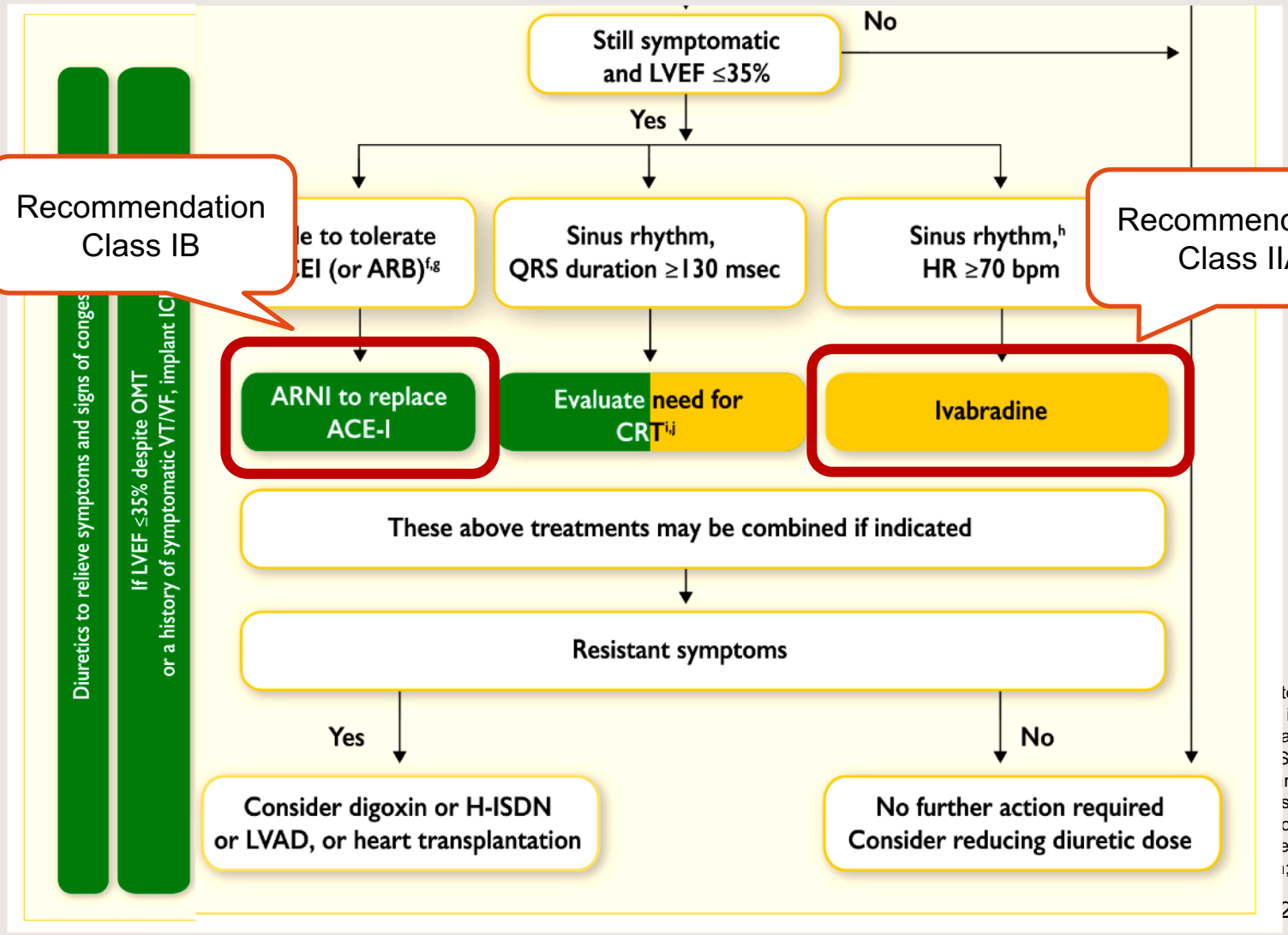


= angiotensin receptor
BNP = B-type natriuretic
= heart failure; HFrEF =
dralazine and isosorbide
defibrillator; LBBB = left
e; LVEF = left ventricular
BNP = N-terminal pro-B
c0iation; OMT = optimal
ventricular tachycardia.

9-2200

2016 ESC Guideline

Therapeutic Algorithm for symptomatic HFrEF



tor; ARB = angiotensin receptor inhibitor; BNP = B-type natriuretic apy; HF = heart failure; HFrEF = SDN = hydralazine and isosorbide rdioverter defibrillator; LBBB = left sist device; LVEF = left ventricular or; NT-proBNP = N-terminal pro-B eart Assoc0iation; OMT = optimal ; VT = ventricular tachycardia.

27): 2129-2200

2017 ACC/AHA/HFSA

Focused Update on New Pharmacological Therapy for Heart Failure

Recommendations for Renin-Angiotensin System Inhibition With ACEi / ARB / ARNI		
COR	LOE	Recommendation
I	ACEi : A	The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality
I	ARB : A	The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema
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
Notes		• ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (III : Harm, B-R) • ARNI should not be administered to patients with a history of angioedema (III Harm, C-EO)

Yancy et al. Circulation 2016;134(13): e282–293

2017 ACC/AHA/HFSA

Focused Update on New Pharmacological Therapy for Heart Failure

Recommendation for Ivabradine

COR	LOE	Recomendation
IIa	Ivabradine : 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

Yancy et al. Circulation 2016;134(13): e282–293

Summary

Heart failure burden disease and **rehospitalization** remains **high** → high cost expenditures

ESC and AHA guidelines : ARNI and ivabradine are **recommended** for heart failure patient **with ejection fraction ≤ 35%** and **persistent symptom**

Ivabradine can be **added** to the **sinus rhythm** patient with **heart rate ≥ 70 bpm**

ARNI can be given to **replace ACE/ARB** in sinus rhythm or atrial fibrillation patient

Physician adherence to the evidence based clinical **guidelines still lack off** → need to improve it

NEW HOPE FOR HEART FAILURE

TREATMENT ?

THANK YOU

A R N I