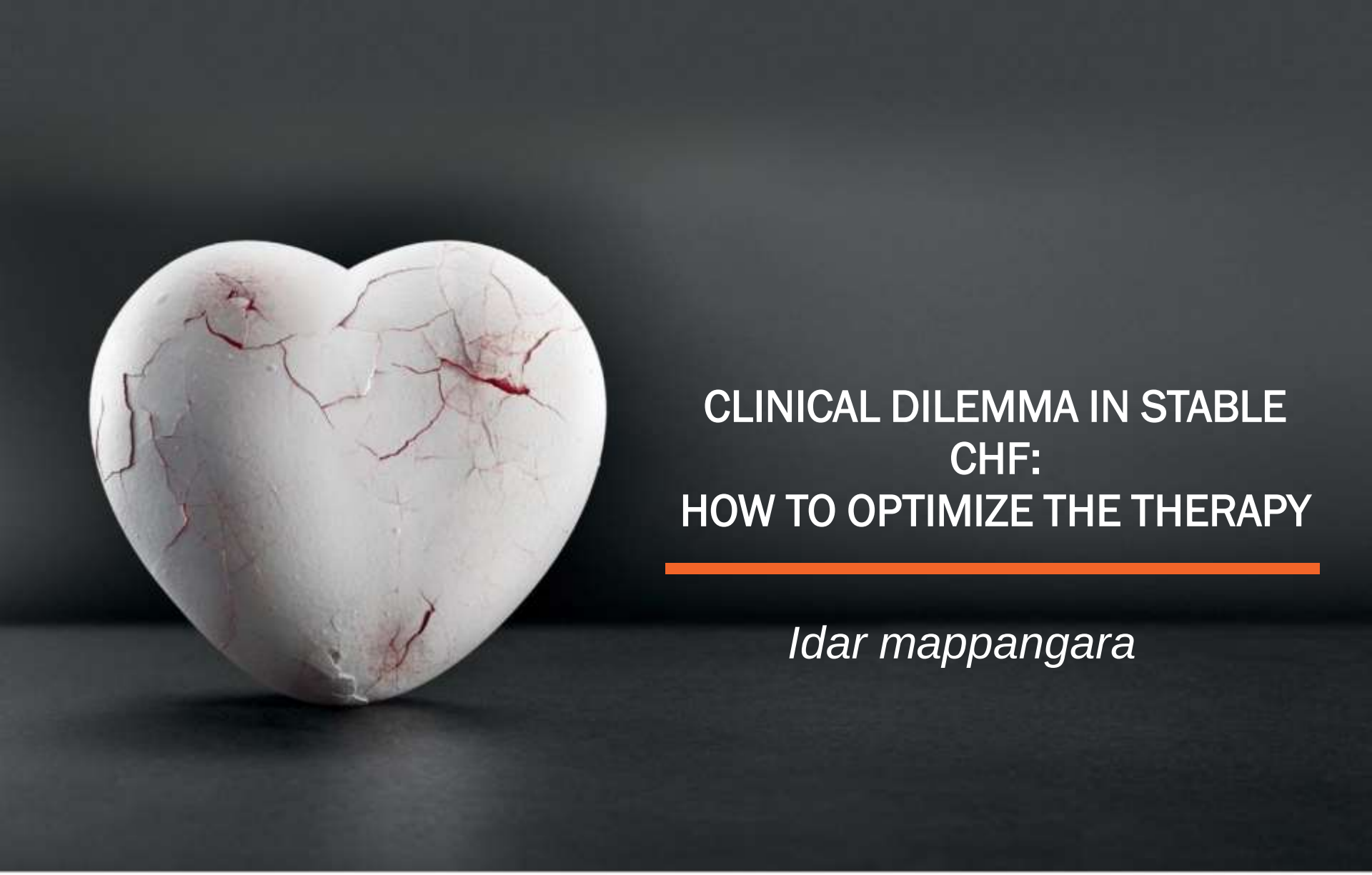


CLINICAL DILEMMA IN STABLE CHF: HOW TO OPTIMIZE THE THERAPY

Idar mappangara

Heart Failure Treatment Goal

ESC 2016

- Improve clinical status
- Improve functional capacity
- Improve quality of life
- Prevent hospital admission
- Reduce mortality

Pedoman Tata Laksana Gagal jantung PERKI 2015

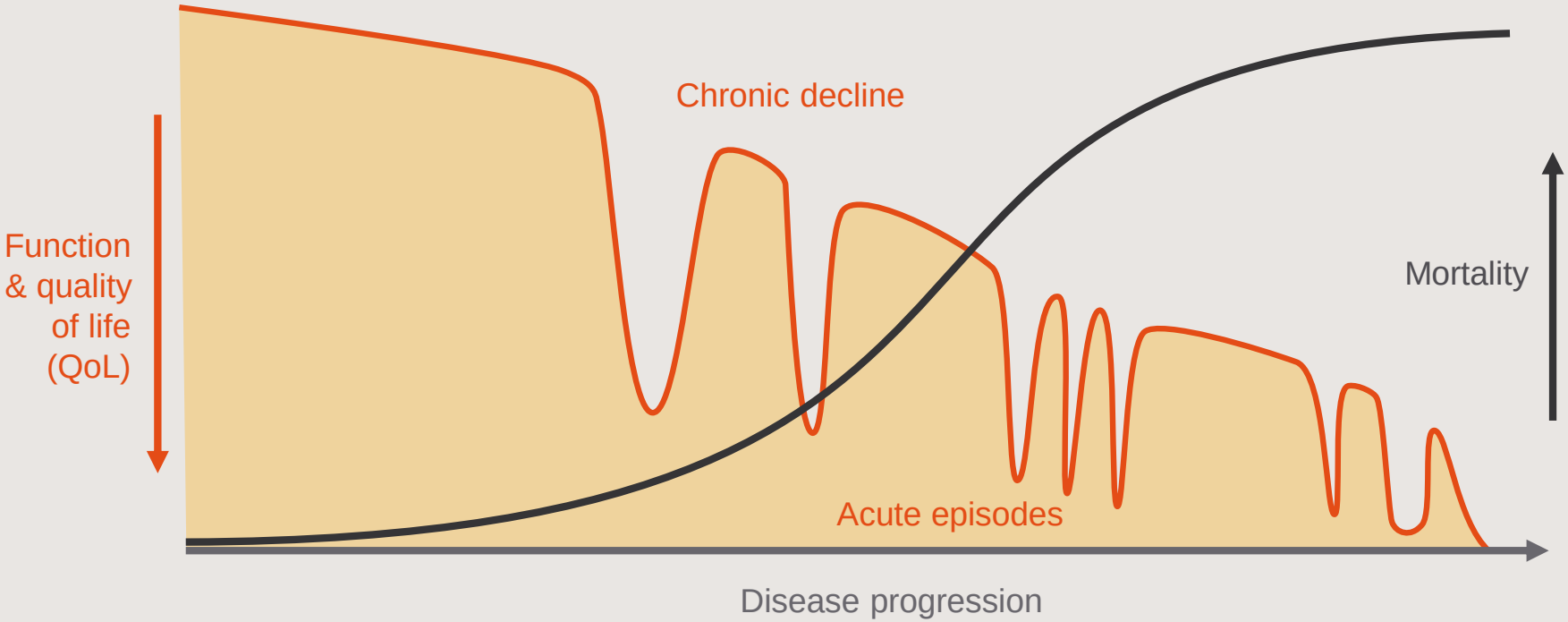
1. Prognosis	**Menurunkan mortalitas**
2. Morbiditas	Meringankan gejala dan tanda Memperbaiki kualitas hidup Menghilangkan edema dan retensi cairan Meningkatkan kapasitas aktifitas fisik Mengurangi kelelahan dan sesak nafas Mengurangi kebutuhan rawat inap Menyediakan perawatan akhir hayat
3. Pencegahan	Timbulnya kerusakan miokard Perburukan kerusakan miokard Remodelling miokard Timbul kembali gejala dan akumulasi cairan Rawat inap

Ponikowski et al. Eur Heart J 2016; 37(27): 2129-2200
Pedoman Tata Laksana Gagal jantung. PERKI 2015

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



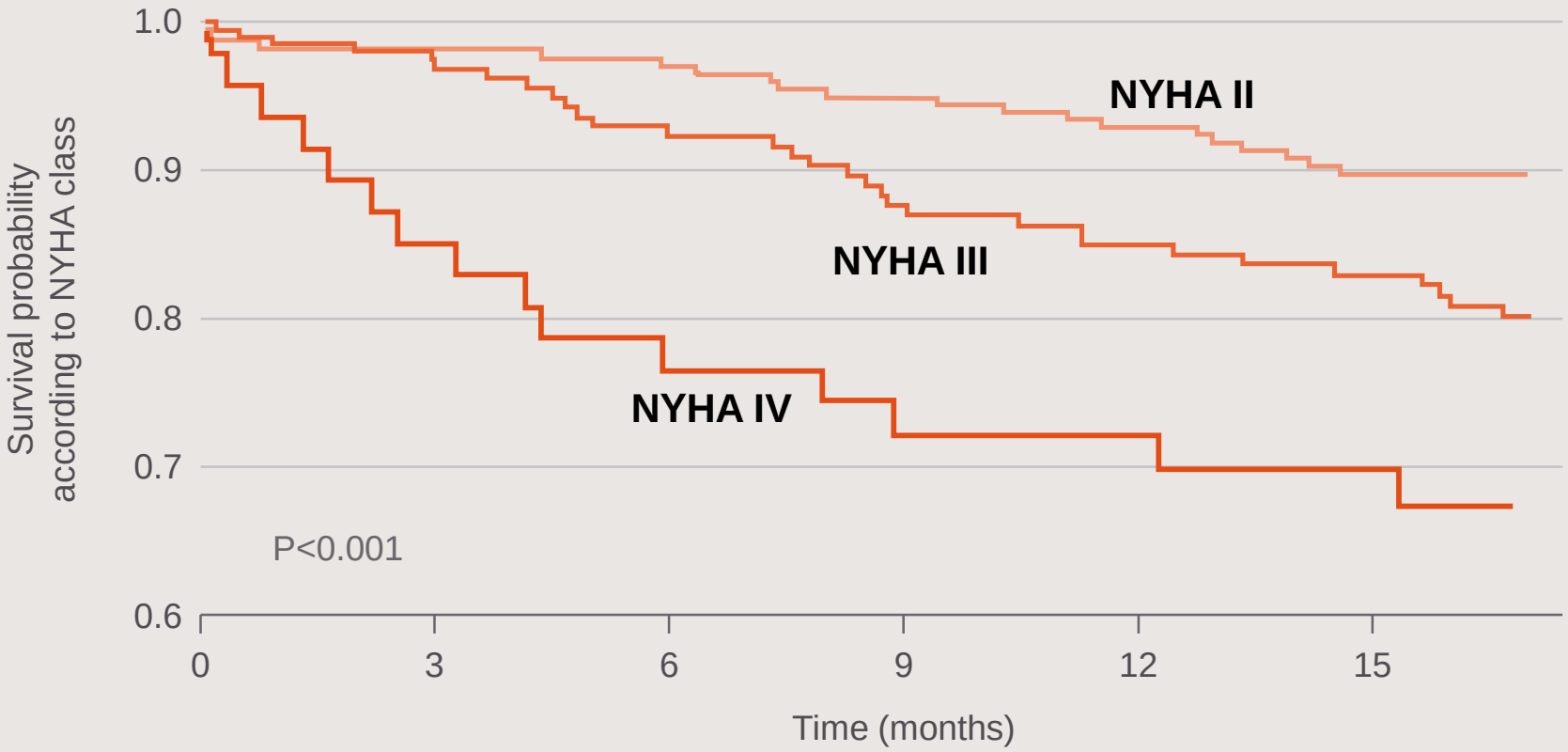
LV: left ventricular

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

NYHA class is related to prognosis in chronic HF

Clinical manifestations

Among 411 outpatients with NYHA class II, III or IV HF, total mortality was 7.1%, 15.0% and 28.0%, respectively during a mean follow-up period of 1.4 years



NYHA: New York Heart Association

Muntwyler et al. Eur Heart J 2002;23:1861–6

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

Activated in response to reduced cardiac output[1]

Short-term effects are beneficial in early HF[1]

Long-term activation exerts unfavourable effects[1,3]

RAAS

NP system

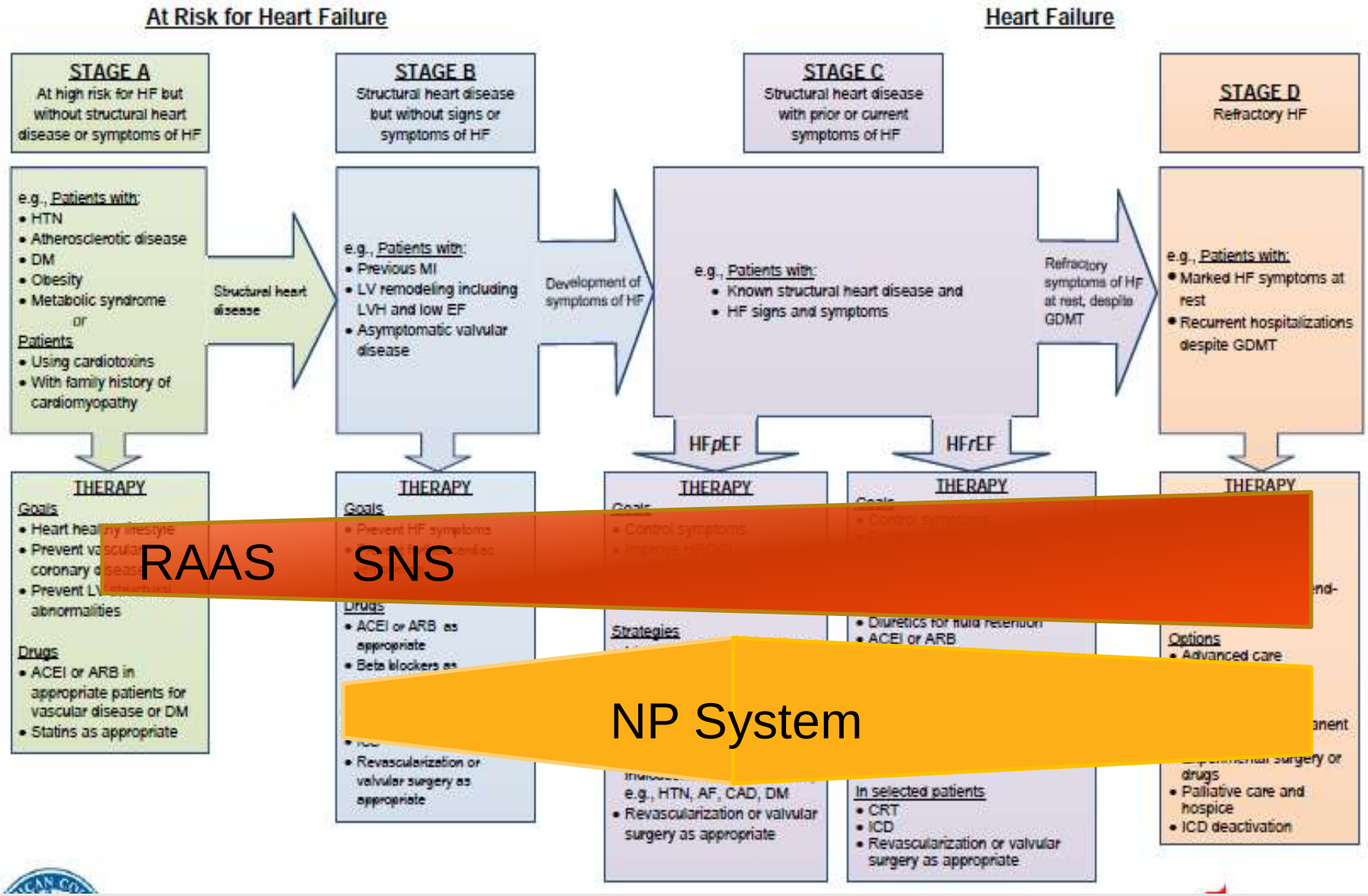
Release of NPs in response to cardiac stress[2]

Opposes the actions of the RAAS[2] and SNS[4,5]

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

Stages, Phenotypes and Treatment of HF



As heart failure advances, the RAAS and SNS become the predominantly activated neurohormonal systems

NP system

NPRs ← NPs

Vasodilation

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

SNS

Epinephrine
Norepinephrine → α_1, β_1, β_2 receptors

Vasoconstriction

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

RAAS

Ang II → AT_1R

Vasoconstriction

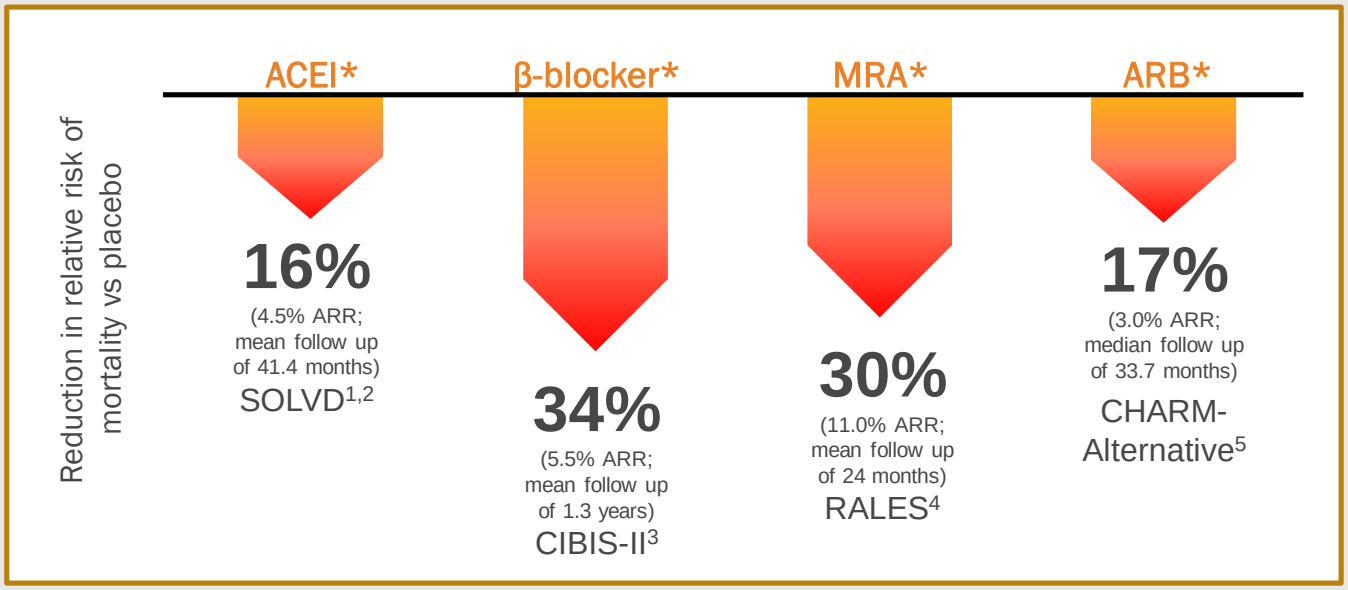
- Blood pressure ↑
- Sympathetic tone ↑
- Aldosterone ↑
- Hypertrophy ↑
- Fibrosis ↑
- Sodium and water retention ↑

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

Mortality remain high despite of the standard HFrEF management

- Survival rates in chronic HF have improved with the introduction of new therapies[1]



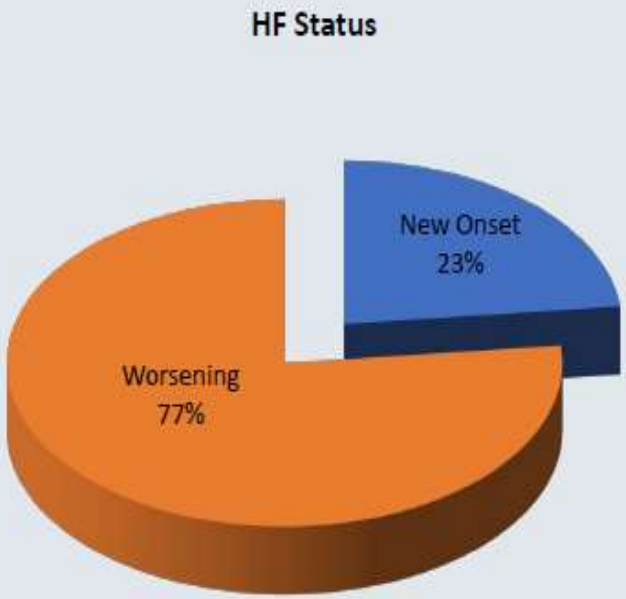
- However, significant mortality remains – ~50% of patients die within 5 years of diagnosis[6–7]

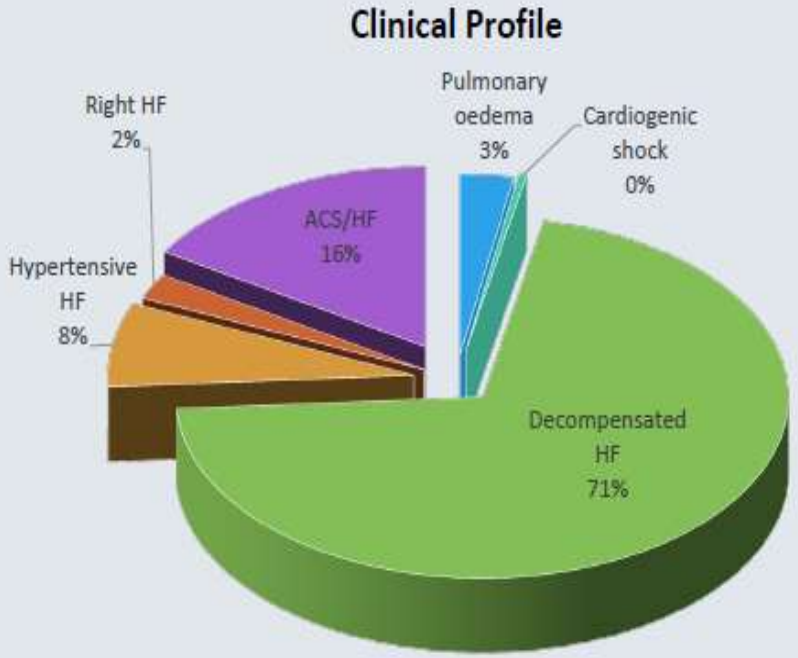
*On top of standard therapy at the time of study (except in CHARM-Alternative where background ACEI therapy was excluded). Patient populations varied between trials and as such relative risk reductions cannot be directly compared. SOLVD (Studies of Left Ventricular Dysfunction), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) and RALES (Randomized Aldactone Evaluation Study) enrolled chronic HF patients with LVEF≤35%. CHARM-Alternative (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) enrolled chronic HF patients with LVEF≤40%

- ACEI=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; HF=heart failure; ARR=absolute risk reduction; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; MRA=mineralocorticoid receptor antagonist

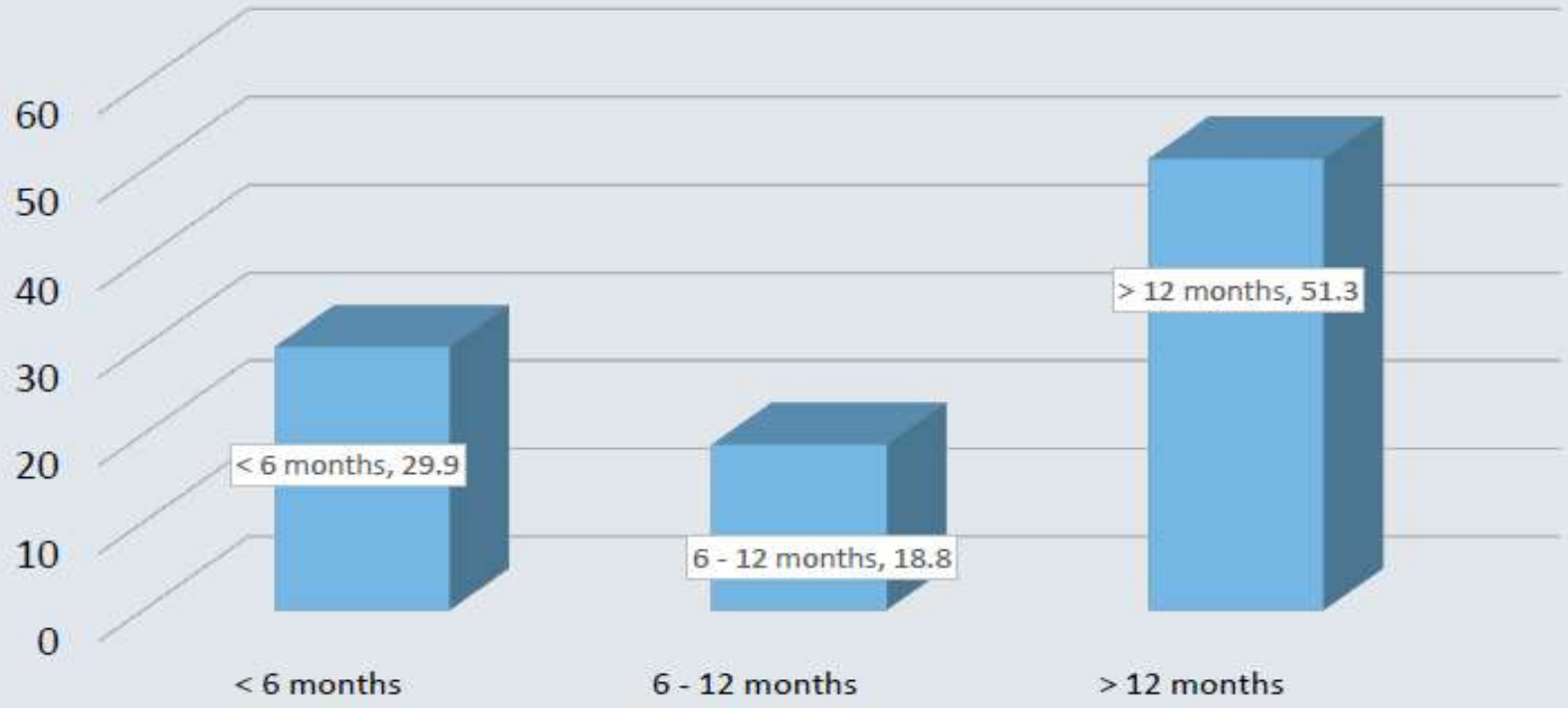
1. McMurray et al. Eur Heart J 2012;33:1787–847; 2. SOLVD Investigators. N Engl J Med 1991;325:293–302; 3. CIBIS-II Investigators. Lancet 1999;353:9–13; 4. Pitt et al. N Engl J Med 1999;341:709-17; 5. Granger et al. Lancet 2003;362:772–66. 6. Yancy et al. Circulation 2013;128:e240–327; 7. Levy et al. N Engl J Med 2002;347:1397–402

Hospital Presentation

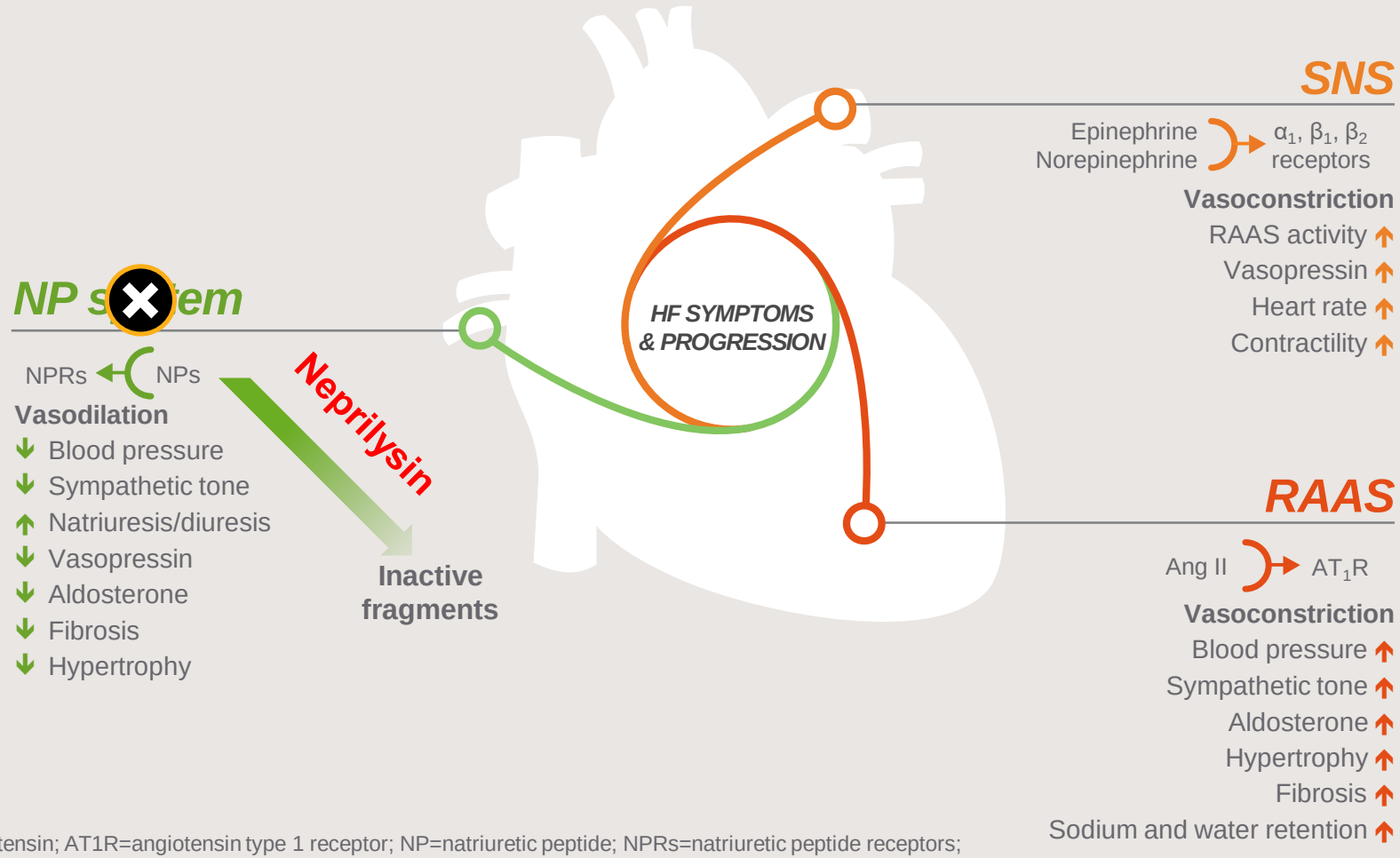




HF Re-hospitalization



NP system counter balance the unfavourable prolonged effect of SNS and RAS, but quickly degraded by Neprilysin

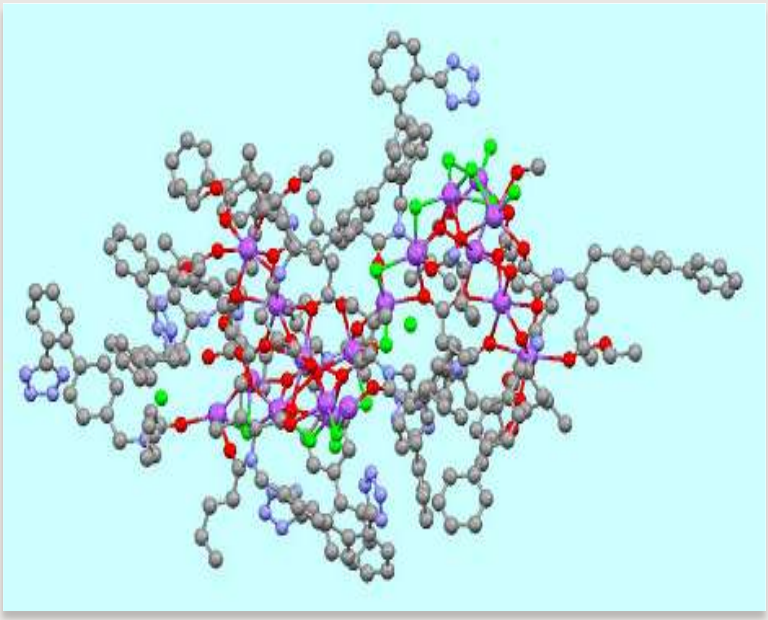


ANG=angiotensin; AT1R=angiotensin type 1 receptor; NP=natriuretic peptide; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

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

Sacubitril Valsartan (LCZ696) is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI)

- Sacubitril Valsartan (LCZ696) is a novel drug which delivers simultaneous neprilysin inhibition and AT_1 receptor blockade[1–3]
- LCZ696 is a salt complex that comprises the two active components in a 1:1 molar ratio:[2,3]
  - sacubitril (AHU377) – a pro-drug; further metabolized to the neprilysin inhibitor LBQ657, and
  - valsartan – an AT_1 receptor blocker

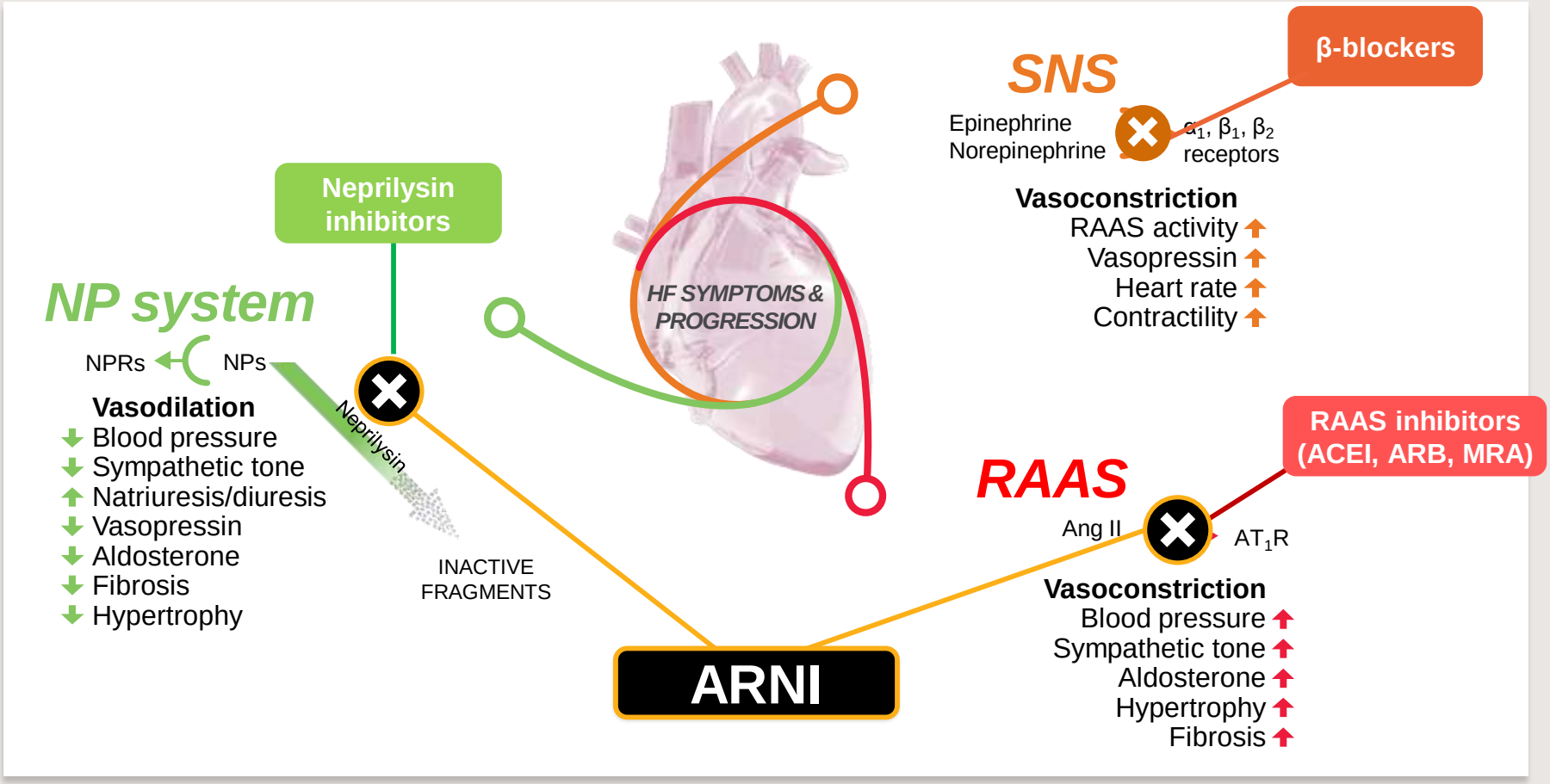


3D LCZ696 structure[2]

ARNI=angiotensin receptor neprilysin inhibitor; AT1=angiotensin II type 1

1. Bloch & Basile. J Clin Hypertens 2010;12:809–12;
2. Gu et al. J Clin Pharmacol 2010;50:401–14;
3. Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9

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

ARNI PIVOTAL STUDY

PARADIGM-HF

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

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ESC 2016

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- Improve functional capacity
- Improve quality of life
- Prevent hospital admission
- Reduce mortality

Pedoman Tata Laksana Gagal jantung PERKI 2015

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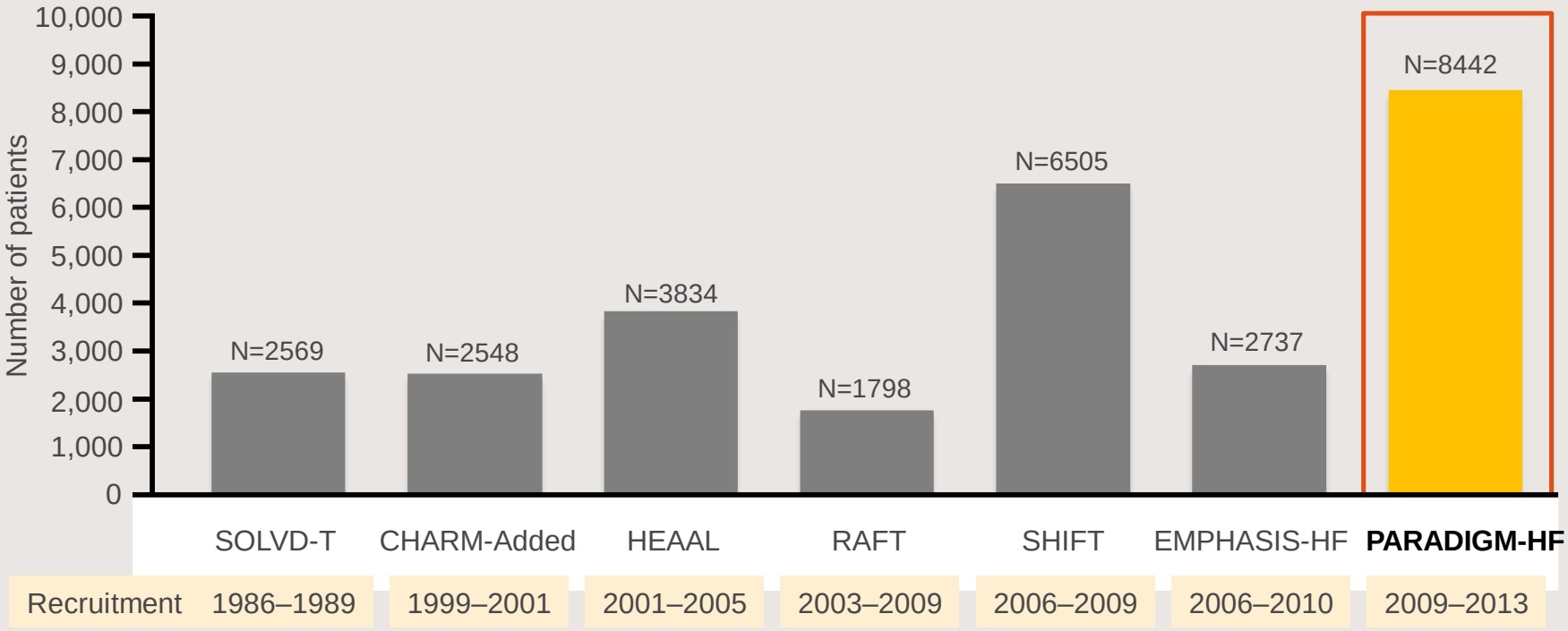
Ponikowski et al. Eur Heart J 2016; 37(27): 2129-2200
Pedoman Tata Laksana Gagal jantung. PERKI 2015

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; RAFT, Resynchronization/Defibrillation for Ambulatory Heart Failure Trial; SHIFT, Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial; SOLVD-T, Studies of Left Ventricular Dysfunction Treatment trial

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

ARNI Clinical Study : PARADIGM-HF

Primary objective : to evaluate the effect of **Sakubitril Valsartan (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**

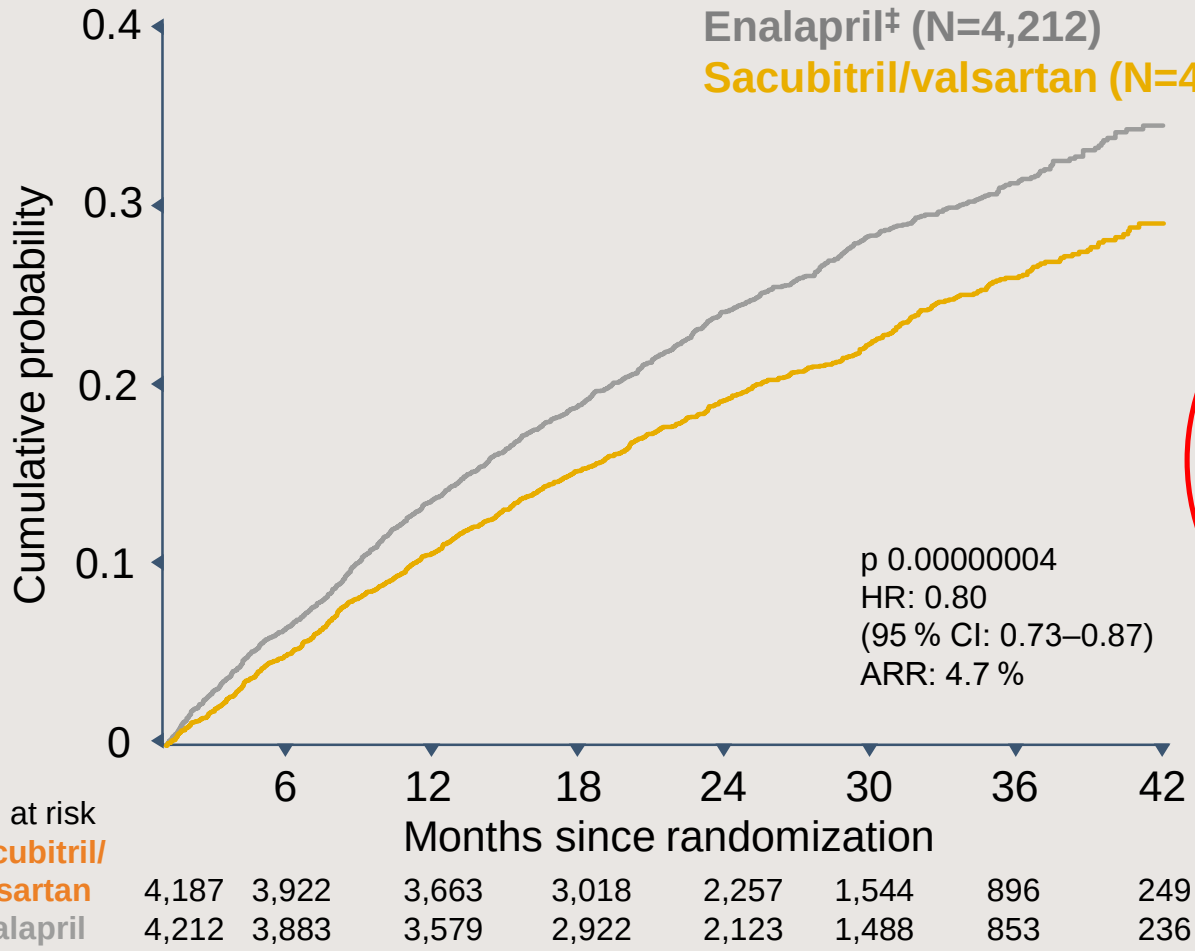
On top of standard HFrEF therapy (excluding ACEIs and ARBs)

*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

Sacubitril/valsartan significantly reduced death from CV causes or first hospitalization for HF*



NNT 21§

20%
RELATIVE RISK REDUCTION OF PRIMARY ENDPOINT

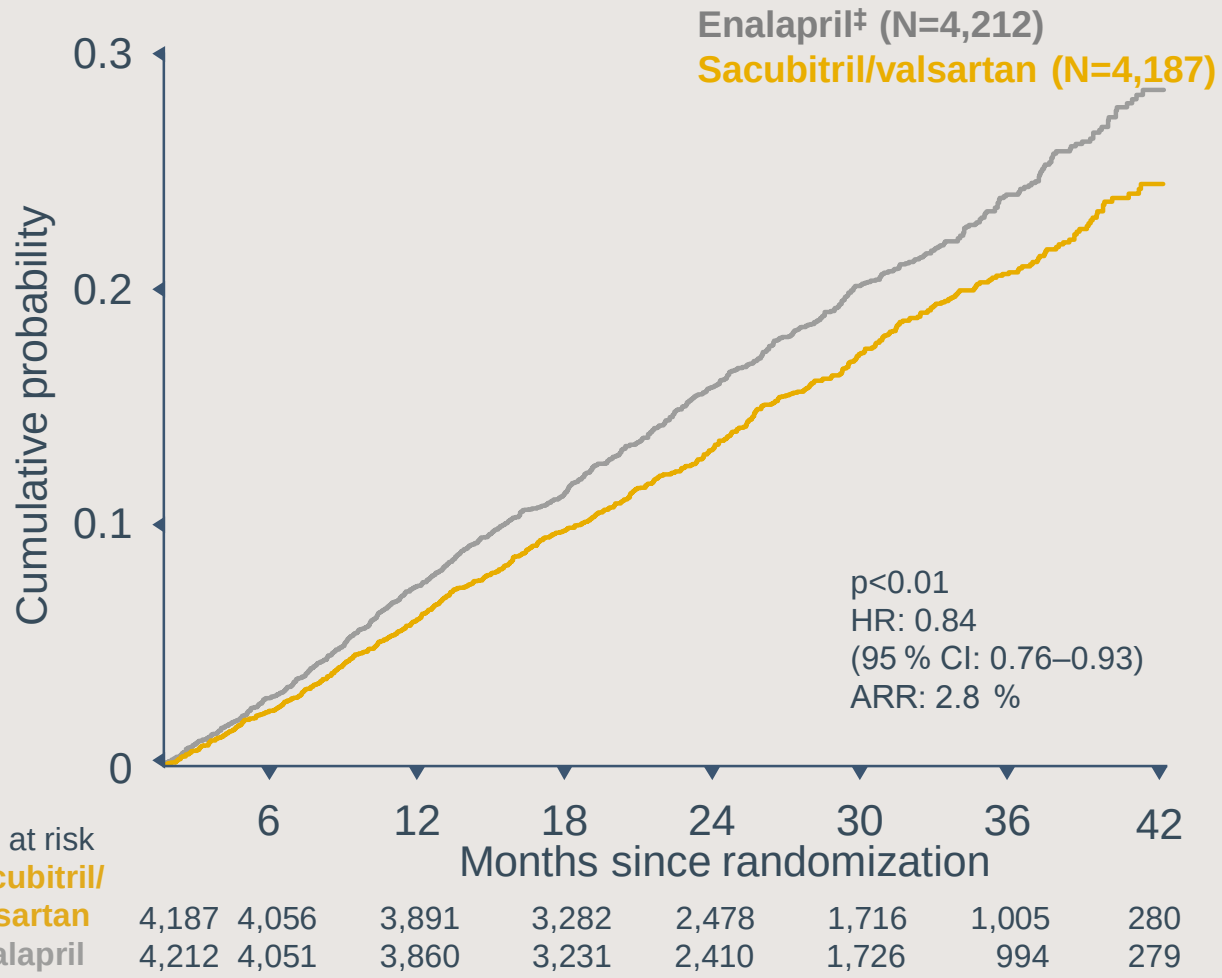
No. at risk								
Sacubitril/valsartan	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

*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

Sacubitril/valsartan significantly reduced all-cause mortality*



NNT 36 §

16%

RELATIVE RISK REDUCTION OF ALL-CAUSE MORTALITY

*Time to all-cause 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; HF=heart failure; HR=hazard ratio; NNT=number needed to treat
McMurray et al. N Engl J Med 2014;371:993–1004

Secondary outcomes – summary

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 [illegible]#	[illegible]	[illegible]6)	0.86 (0.65–1.13)	0.28

Superior in reducing death from any cause
Improve patient quality of life

*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

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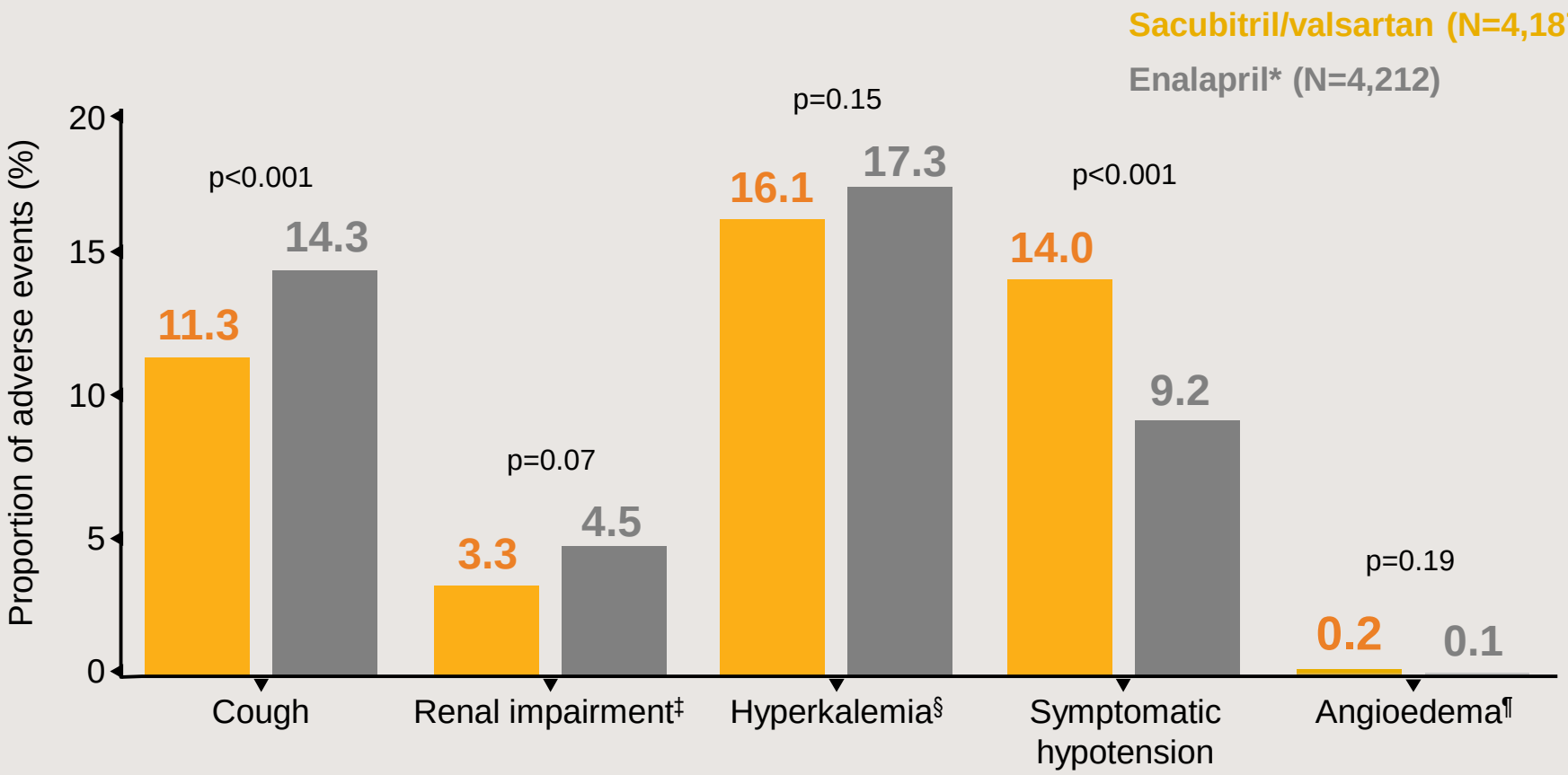
New onset atrial fibrillation¶, n (%)	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function#, n (%)	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

Same safety on AF and renal function as ACEi

*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

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

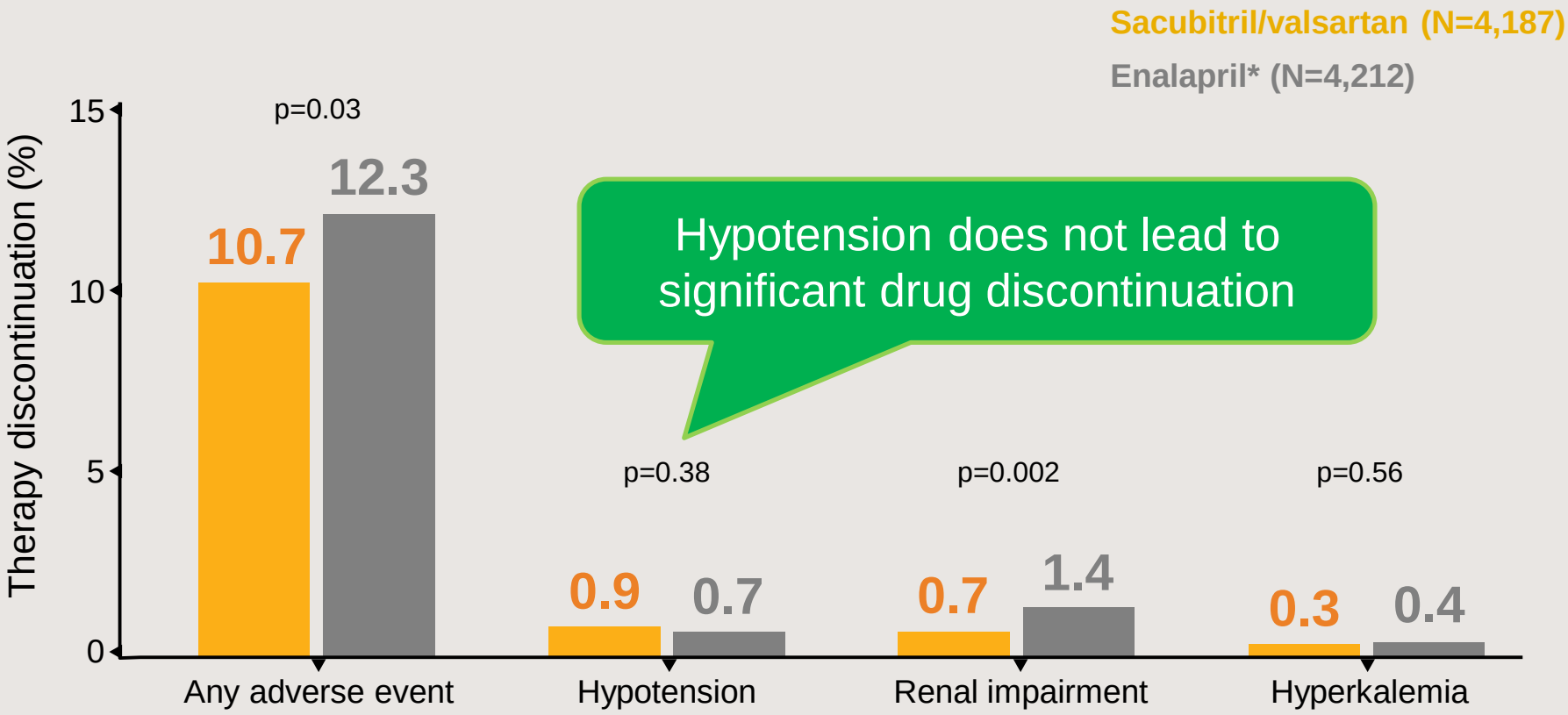
Four most frequently reported adverse reactions and incidence of angioedema in PARADIGM-HF



*Enalapril 10 mg 2x daily as comparator vs sacubitril/valsartan 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy); ‡Elevated serum creatinine ≥2,5 mg/dL; §Elevated serum potassium >5,5 mmol/l; ¶Angioedema with no treatment or use of antihistamines only

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

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



76% of patients remained on the target dose of sacubitril/valsartan (200 mg 2x daily) until the end of the study[2]

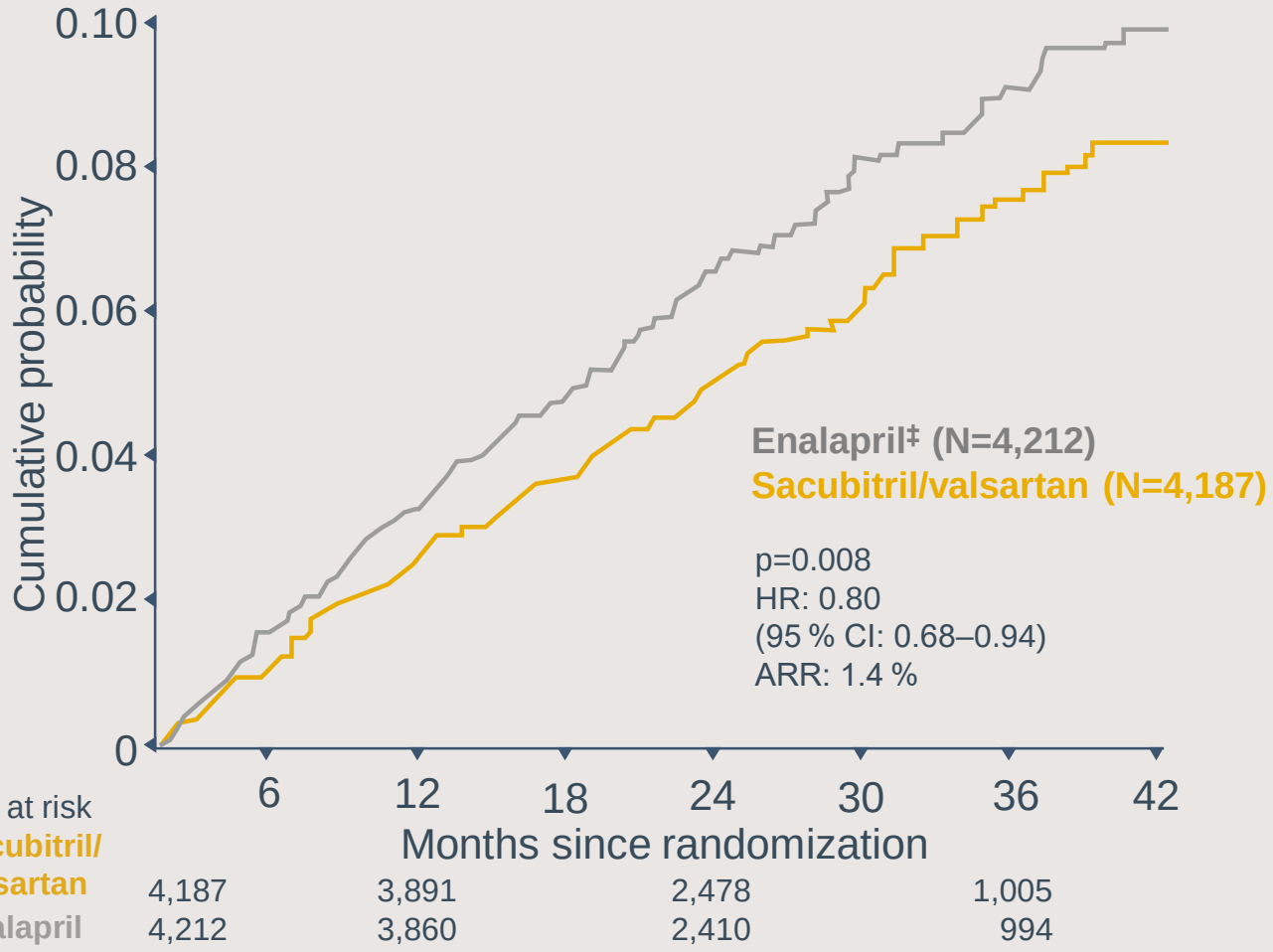
*Enalapril 10 mg 2x daily as comparator vs sacubitril/valsartan 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy)

1. McMurray et al. N Engl J Med 2014;371:993–1004; 2. Packer et al. Circulation 2015;131:54–61

PARADIGM-HF

additional mortality & Morbidity data

Sacubitril/valsartan significantly reduced the risk of sudden death[1]



NNT 71 §

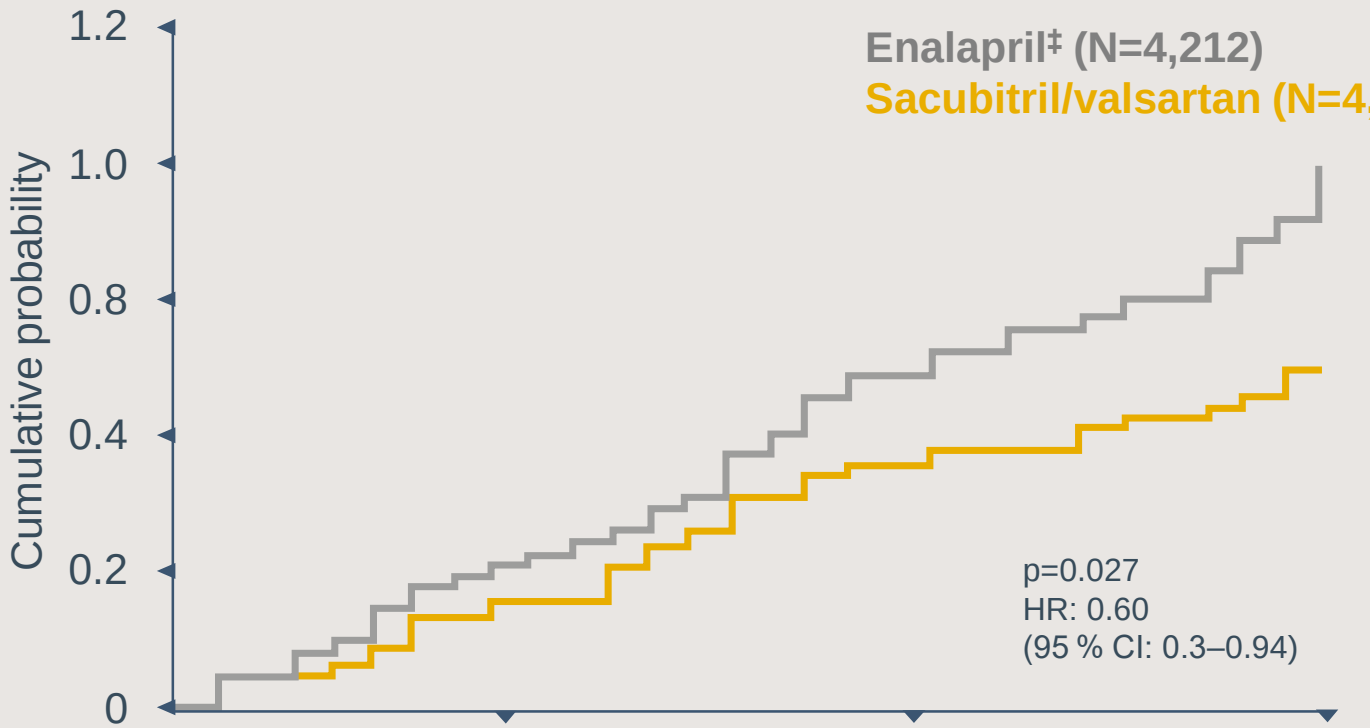
20%

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

Sacubitril/valsartan significantly reduced the risk of first hospitalization for HF within the first 30 days after randomization*



40%

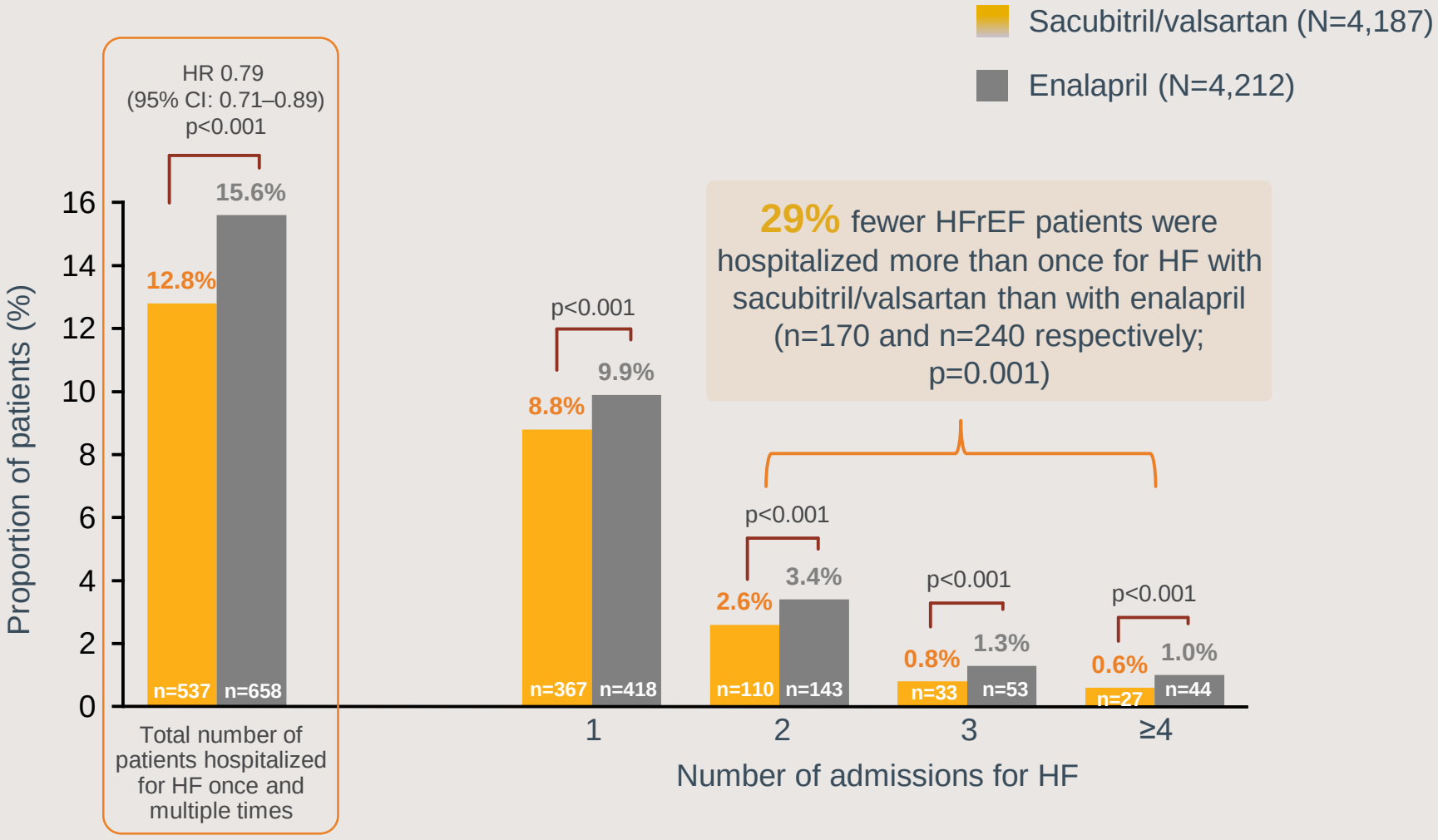
RELATIVE RISK REDUCTION OF FIRST HOSPITALIZATION In the first 30 days

No. at risk				
Sacubitril/valsartan	4,187	4,174	4,153	4,140
Enalapril	4,212	4,192	4,166	4,143

*Time to first hospitalization for HF; ‡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; HF=heart failure; HR=hazard ratio

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

Treatment with sacubitril/valsartan resulted in a lower likelihood of multiple hospitalizations for HF



CI=confidence interval; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; HR=hazard ratio

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

Landmark trials in patients with HFrEF

SOLVD-T[1] (1991)
2,569 patients
Key benefits of enalapril (ACEI) vs placebo:
- 16% ↓ all-cause mortality

CHARM-Alternative[3] (2003)
2,028 patients
Key benefits of candesartan (ARB) vs placebo:
- 23% ↓ CV mortality or HF hospitalization

SHIFT[5] (2010)
6,558 patients
Key benefits of ivabradine (I_f inhibitor) vs placebo:
- 18% ↓ CV death or HF hospitalization

PARADIGM-HF[7] (2014)
8,442 patients
Key benefits of (ARNI) vs enalapril:
- 20% ↓ CV mortality or HF hospitalization

1990s **2000s** **2010s**

CIBIS-II[2] (1999)
2,647 patients
Key benefits of bisoprolol (BB) vs placebo:
- 34% ↓ all-cause mortality

CHARM-Added[4] (2003)
2,548 patients
Key benefits of candesartan (ARB) vs placebo:
- 15% ↓ CV mortality or HF hospitalization

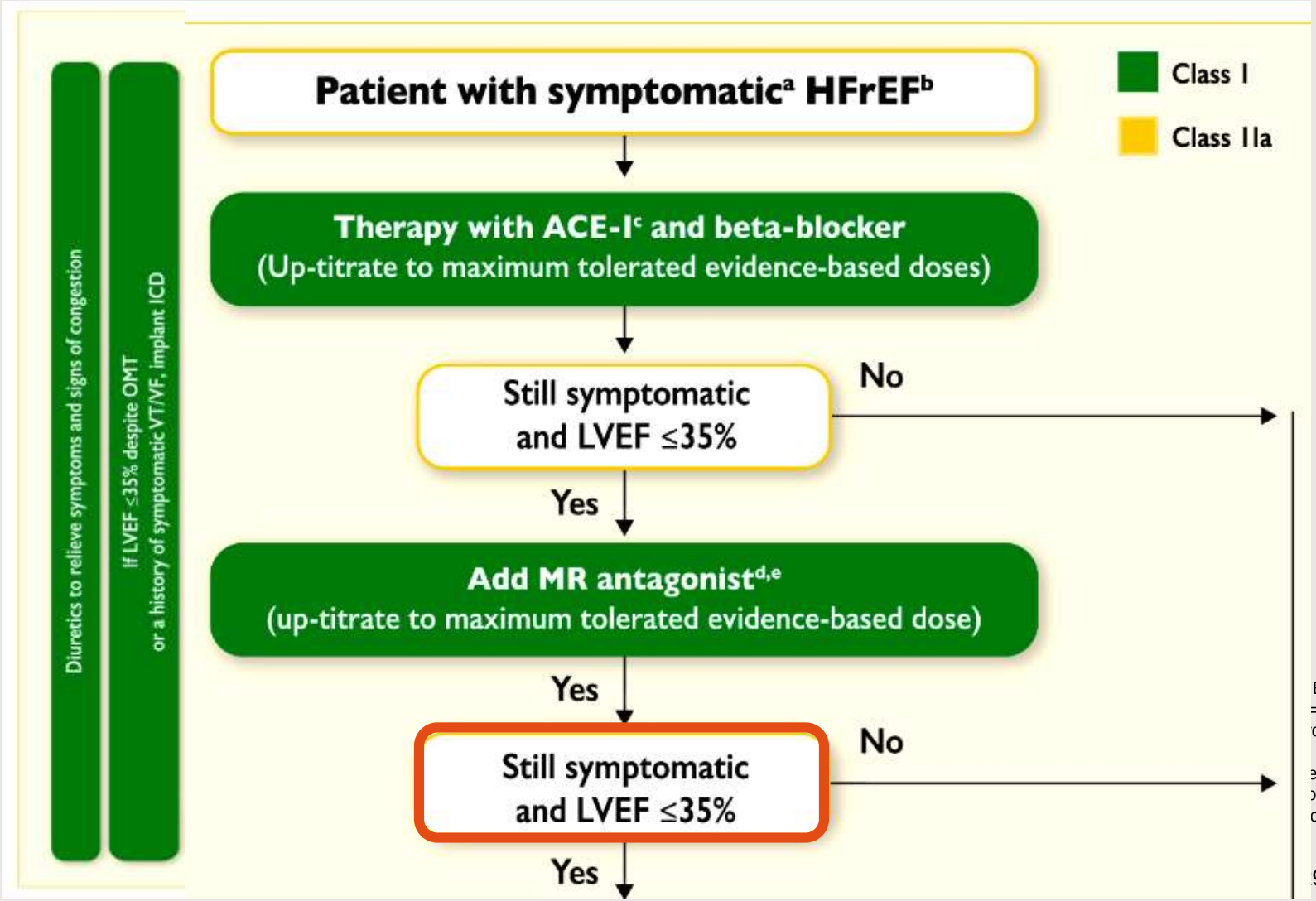
EMPHASIS-HF[6] (2011)
2,737 patients
Key benefits of eplerenone (MRA) vs placebo:
- 37% ↓ CV mortality or HF hospitalization

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

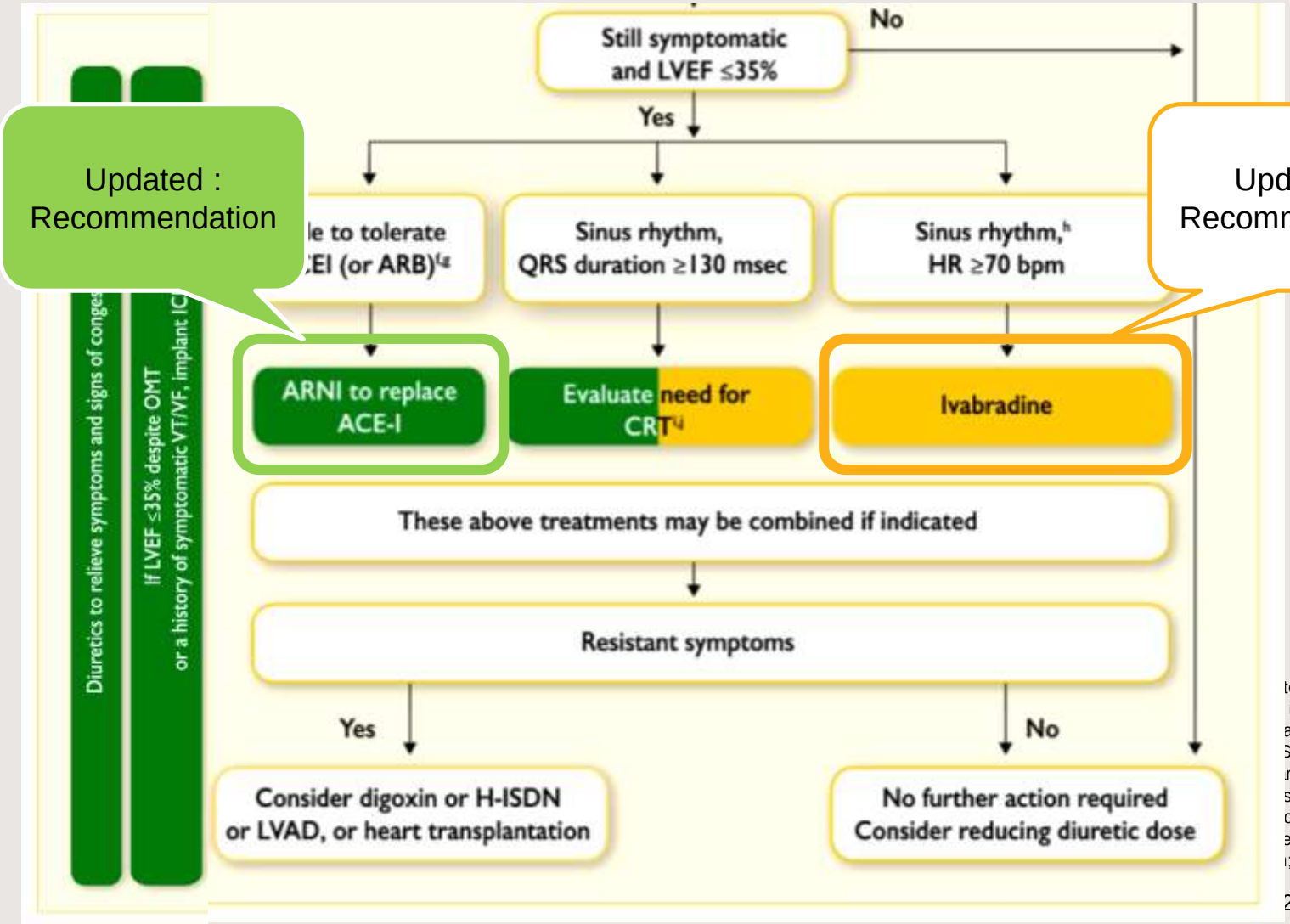
2016 ESC Guideline
Therapeutic algorithm for HFrEF



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

9-2200

2016 ESC Guideline
Therapeutic algorithm for HFrEF



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27): 2129-2200

2016 ACC/AHA/HFSA

Focused Update on New pharmacological Therapy for Heart Failure

Recommendations for Renin-Angiotensin System Inhibition With ACEi / ARB / ARNI

COR	LOE	Recomendation
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)

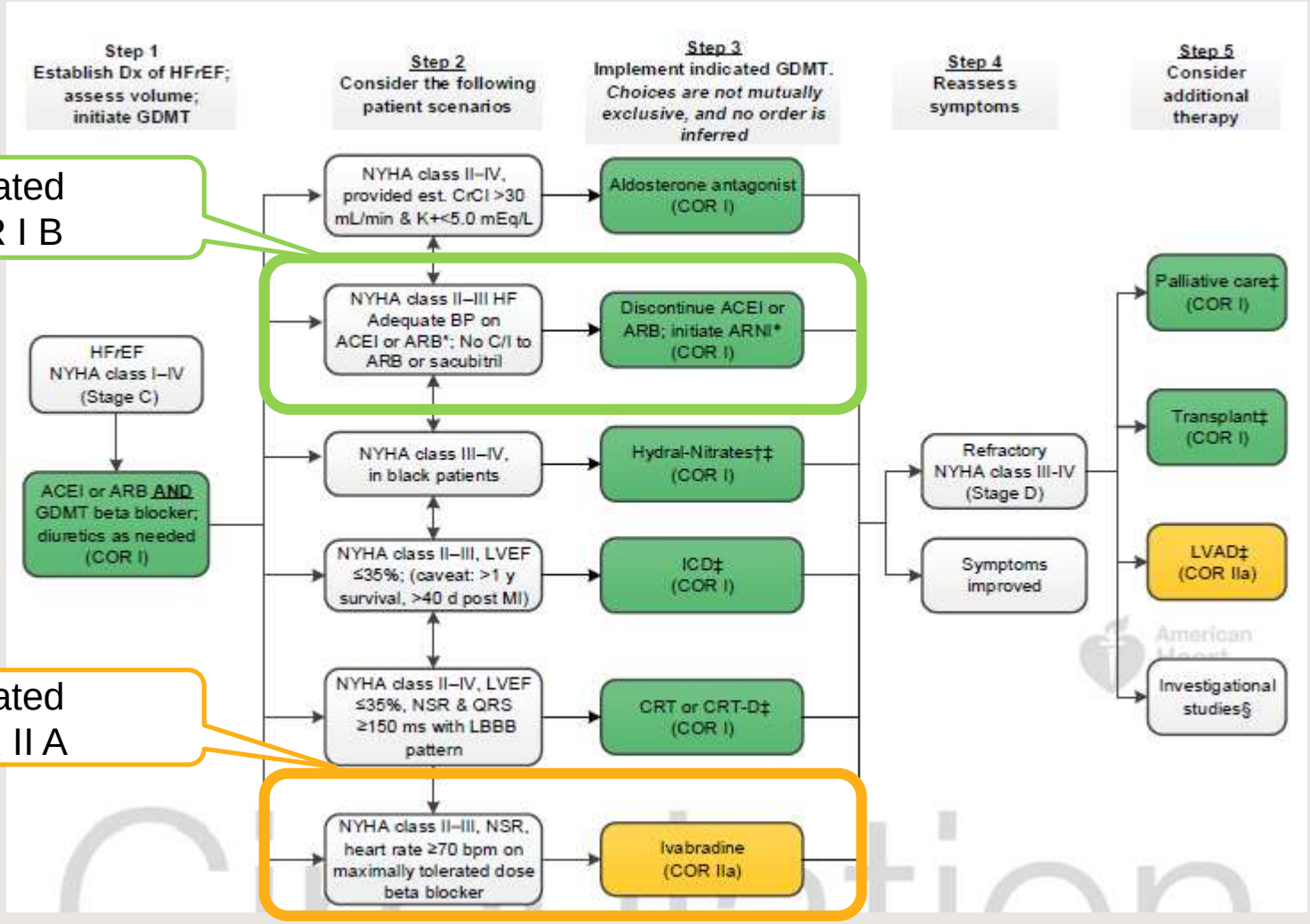
Recommendation for Ivabradine

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

2017 ACC/AHA/HFSA

Focused Update on New pharmacological Therapy for Heart Failure



Yancy et al. Circulation. 2017;136:e137-e161

Summary

- NYHA class has correlation with mortality rate, in 1.4 years mortality was :
  - 7.1% for NYHA class II
  - 15.0% for NYHA class II
  - 28.0% for NYHA class III
- ARNI (Sacubitril Valsartan) inhibit NP degradation by neprilisin when simultantly blocking AT_1R, restoring the balance of neurohormonal system
- PARADIGM-HF was stopped early due to strong finding that Sacubitril Valsartan was superior to ACEi in :
  - Reducing 20% CV mortality
  - Reducing 21% first hospitalization of HF
  - Well tolerated safety profile
- Sacubitril Valsartan is recommended (class I) by guidelines to replace ACEi/ARB in symptomatic HFrEF patient

THANK YOU