The role of ARNI in HFrEF management

From PARADIGM-HF to real world evidence.

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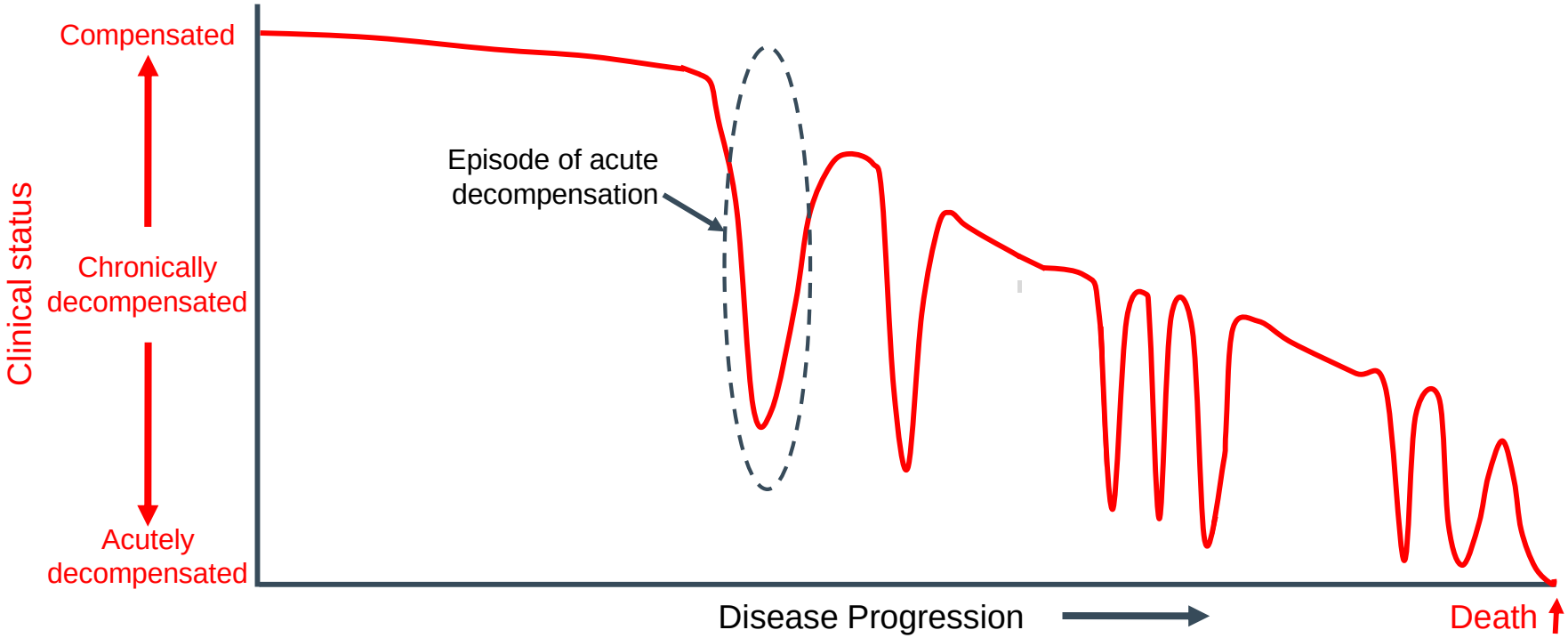
2018-09-01



Heart failure is a progressive disease whereby cardiac structure and function continue to deteriorate

- Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality[1–7]



Adapted from Gheorghiade et al. 2005[2]

HF, heart failure

1. Ahmed et al. Am Heart J 2006;151:444–50; 2. Gheorghiade et al. Am J Cardiol 2005;96:11G–17G; 3. Gheorghiade, Pang. J Am Coll Cardiol 2009;53:557–73; 4. Holland et al. J Card Fail 2010;16:150–6; 5. Muntwyler et al. Eur Heart J 2002;23:1861–6; 6. McCullough et al. J Am Coll Cardiol 2002;39:60–9; 7. McMurray JJ. et al. Eur Heart J. 2012;33(14):1787–1847

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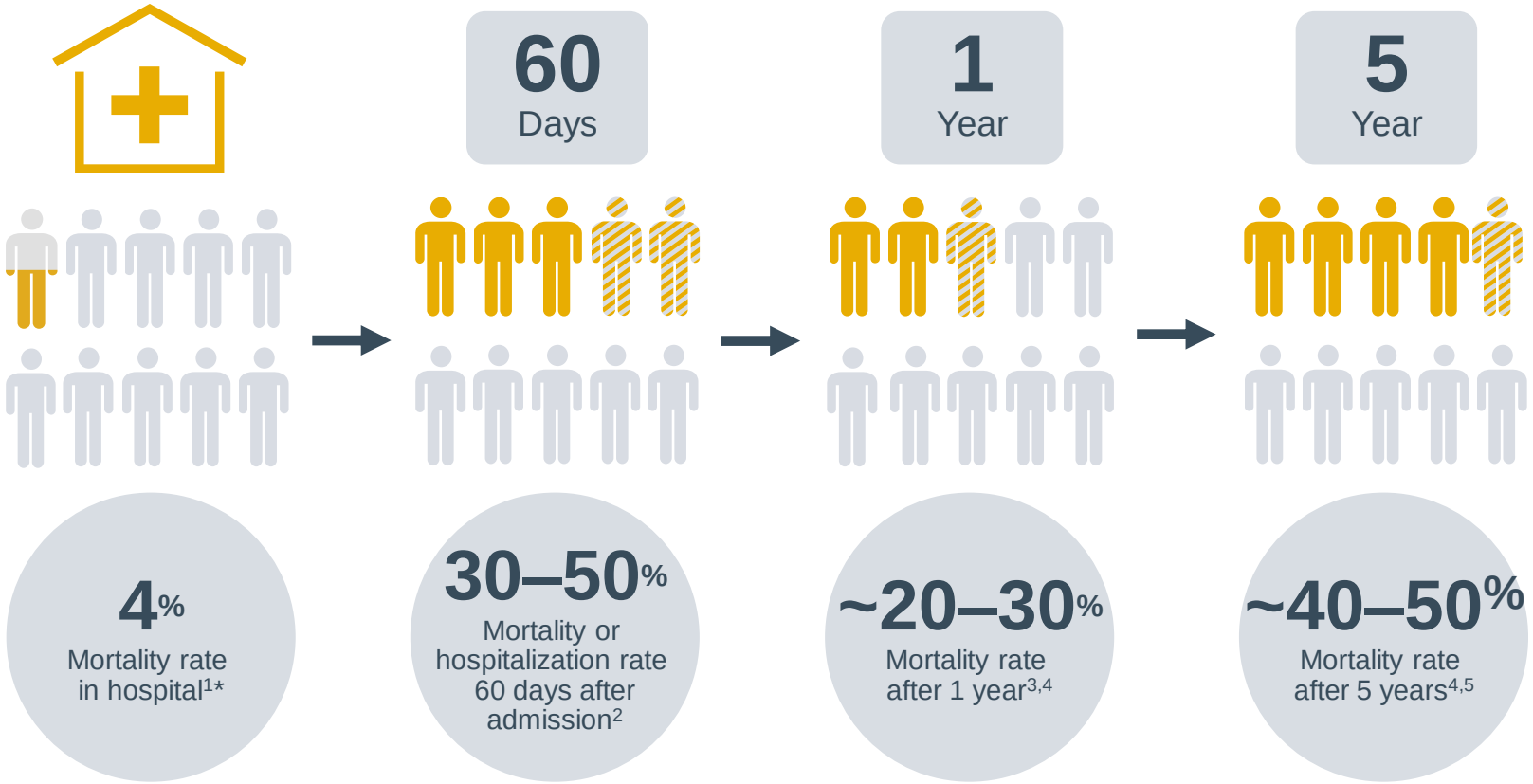
HFrEF is characterized by frequent hospitalization and linked to higher mortality[1–5]



~50% of heart failure deaths occur suddenly[6]

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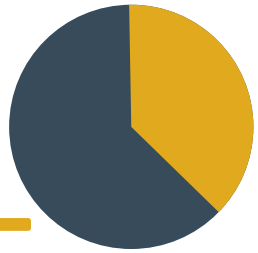
Heart Failure Mortality Statistics for NYHA Class I/II versus Class III/IV

All heart failure patients, even those who are considered asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II), are at high risk of dying[1]

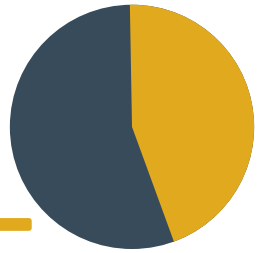
IN A CLINICAL TRIAL WITH MEDIAN FOLLOW-UP OF ~3YEARS

34%



OF NYHA CLASS I AND II PATIENTS DIED

42%



OF NYHA CLASS III AND IV PATIENTS DIED

The neurohormonal imbalance that causes the disease to progress is present in all heart failure patients, even in those who are considered asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II).[1-3]

1. Ahmed A. A propensity matched study of New York Heart Association class and natural history end points in heart failure. Am J Cardiol. 2007;99(4):549-553. 2. Fauci AS, Braunwald E, Kasper DL, et al, eds. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2008. 3. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):e240-e327.

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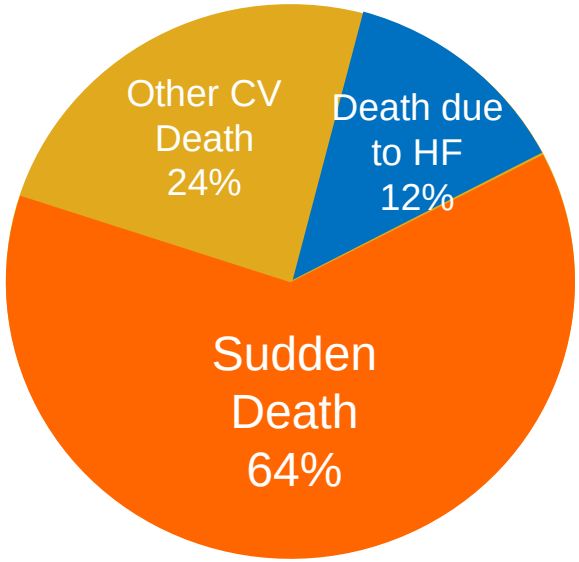
Despite Novel medical therapy, patients with HF are at high risk of sudden cardiac death

- *MERIT HF post hoc analysis*: the incidence of SUDDEN DEATH is higher in patients with less severe HF (NYHA class II), although total mortality rates increase with higher NYHA class[1]

NYHA Class II: Mode of CV death



Number of Death=103
Mean follow up, 1 year

MERIT-HF, 1997[1]
N=3991

CV, cardiovascular; HF, heart failure; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure; NYHA, New York Heart Association;

1.MERIT-HF Study Group. Lancet. 1999;353(9169):2001–7;

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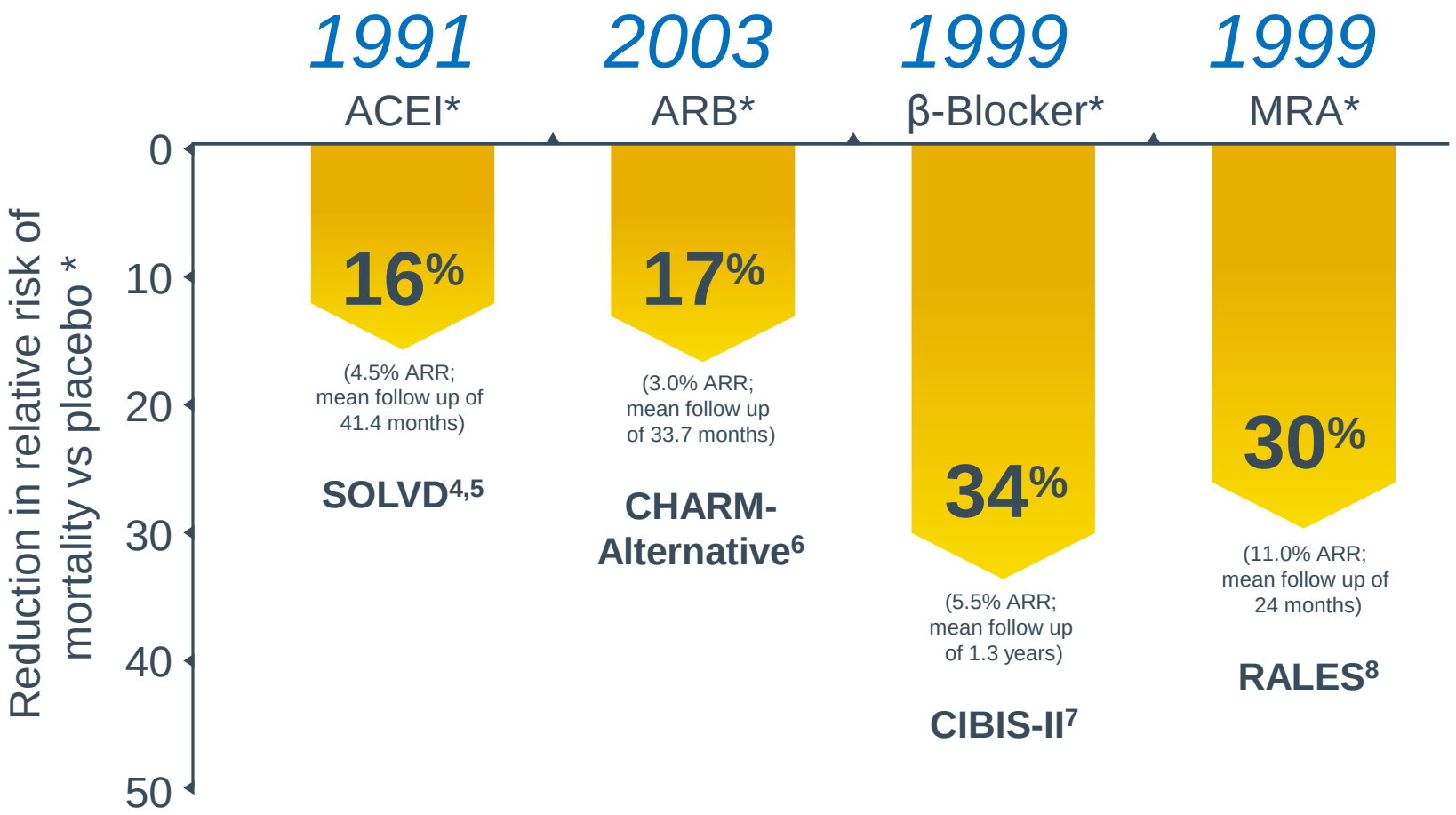
Mortality in HFrEF remains high despite the current therapies that improve survival, versus placebo[1–4]



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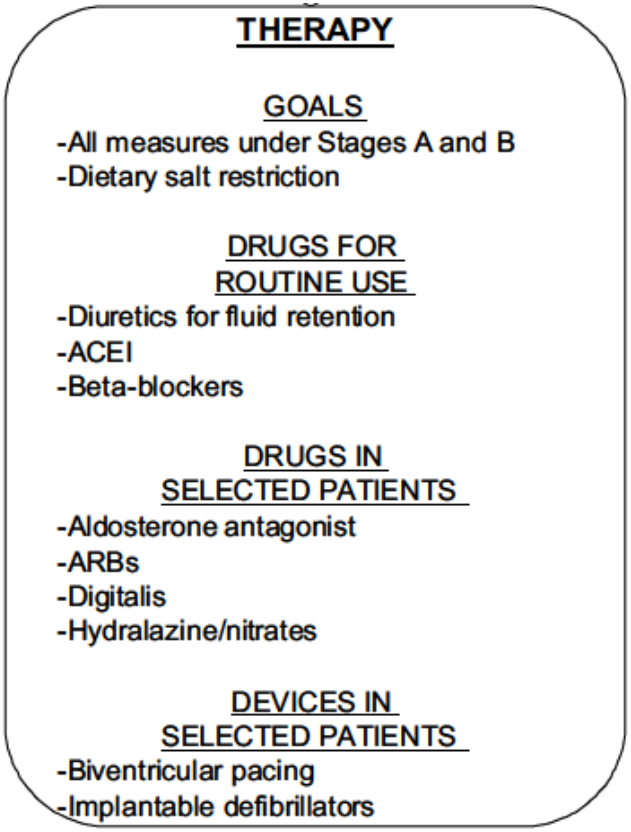
2005 & 2009 ACCF/AHA guideline recommendations for the treatment of patients with HFrEF

HFrEF Stage C
Structural heart disease
with prior or current
symptoms of HF.



Circulation. 2009 Apr 14;119(14):1977-2016

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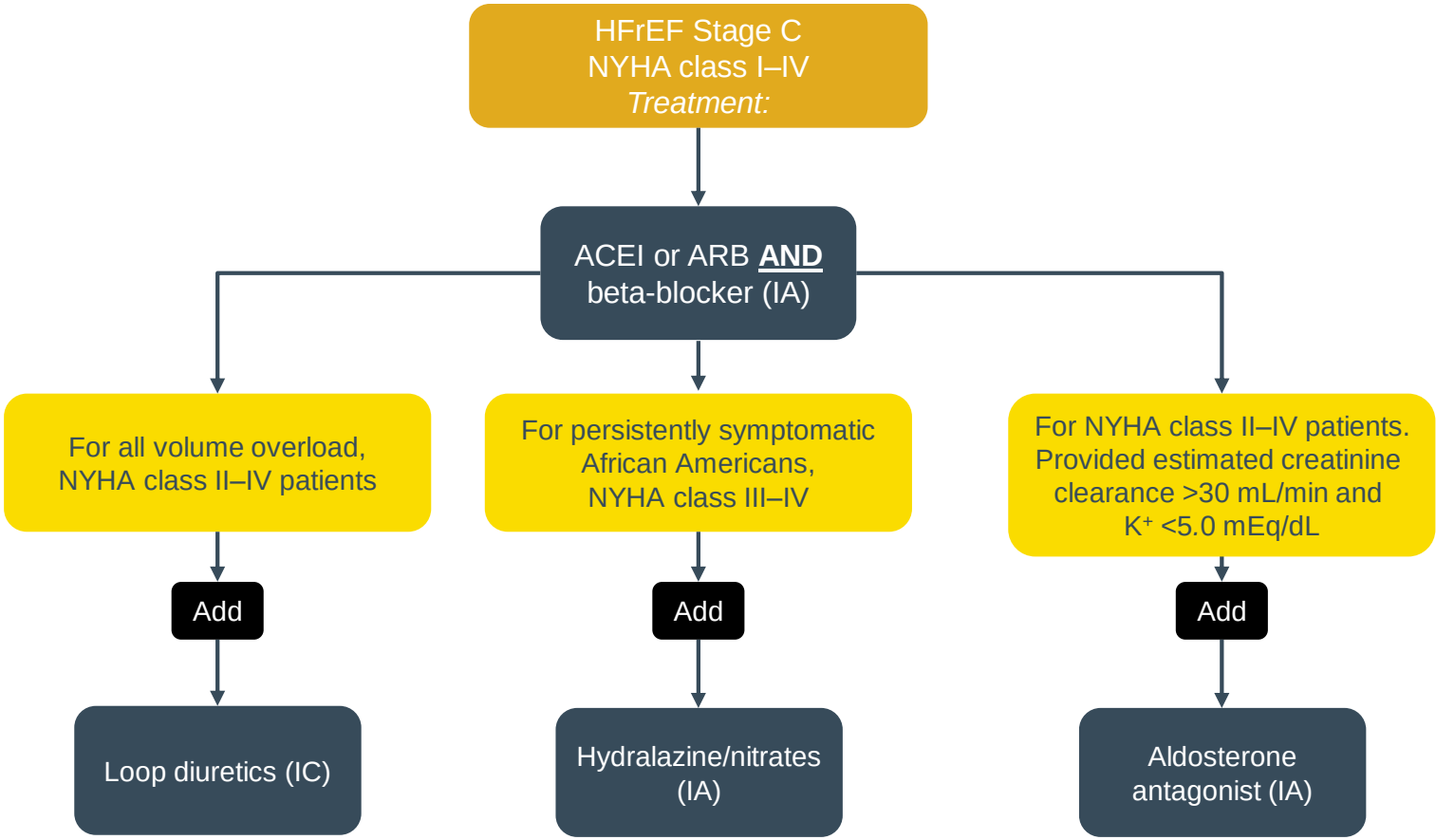
2013 ACCF/AHA guideline recommendations for the treatment of patients with HFrEF

Therapeutic algorithm



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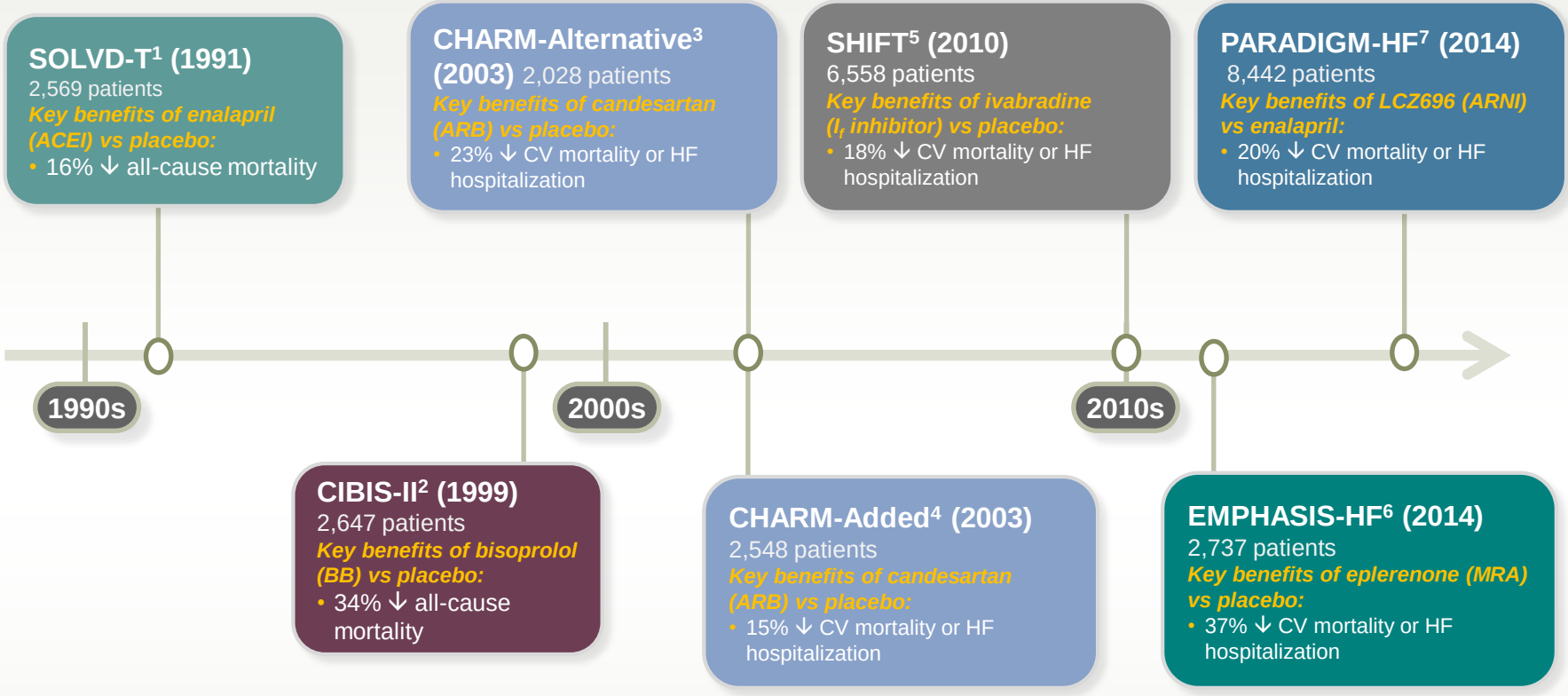
Landmark trials in patients with HFrEF



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;362:767–71; 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

The NEW ENGLAND JOURNAL of MEDICINE

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

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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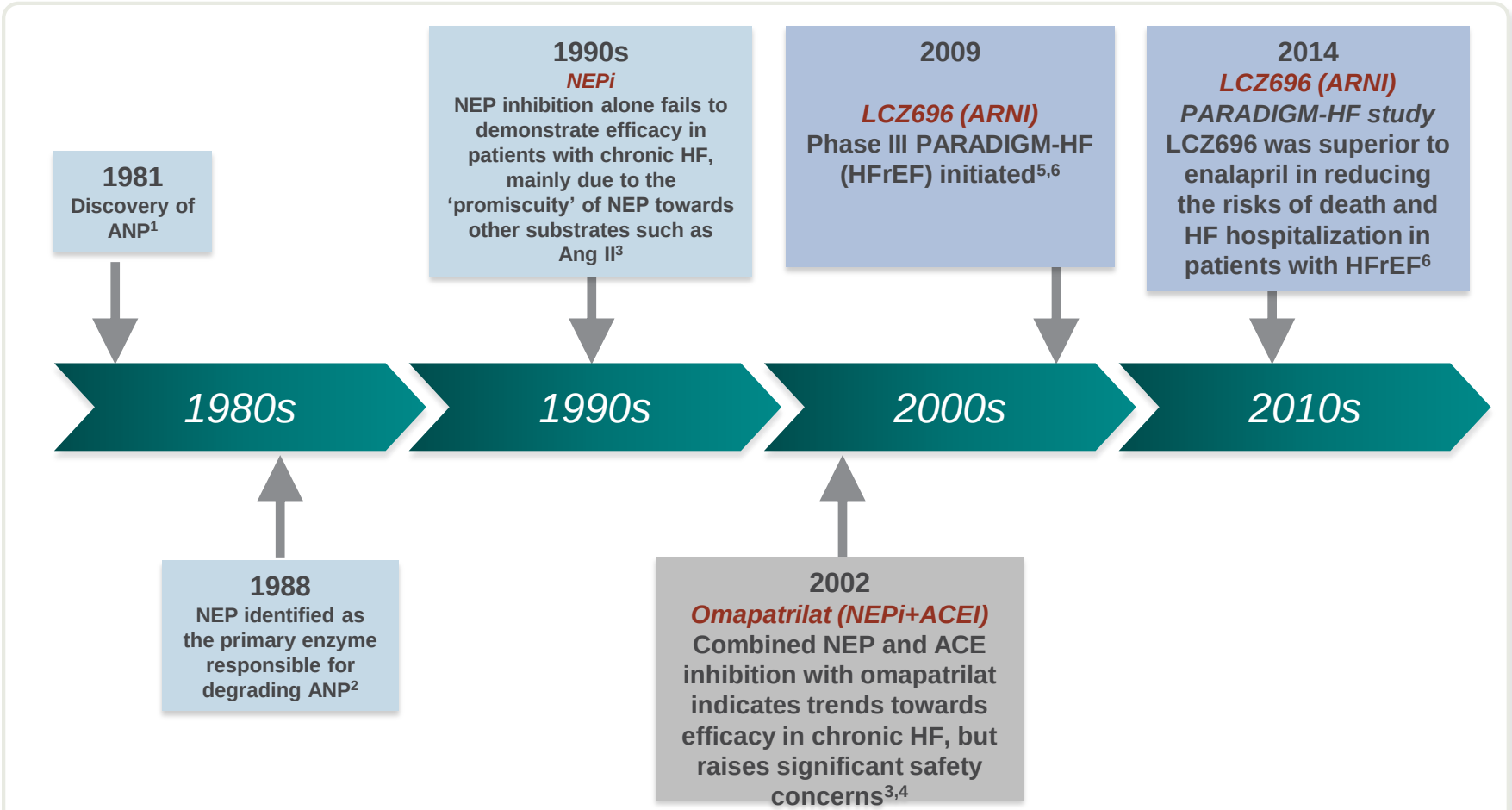
CONCLUSIONS

LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

N Engl J Med. 2014 Sep 11;371(11):993-1004

LCZ696 is the first agent to demonstrate a significant clinical benefit with NP system enhancement in chronic HF with reduced ejection fraction

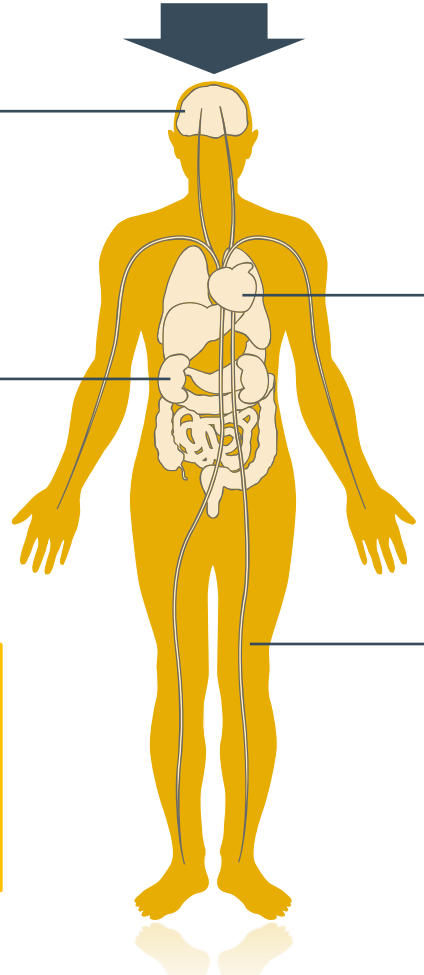


ACE: angiotensin-converting enzyme; ACEI: angiotensin-converting-enzyme inhibitor; Ang: angiotensin; ANP: atrial natriuretic peptide; ARNI: angiotensin receptor neprilysin inhibitor; AT_1R: angiotensin II type 1 receptor; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; NEP: neprilysin; NEPi: neprilysin inhibition; NP: natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

1. de Bold et al. Life Sci 1981;28:89–94; 2. Sonnenberg et al. Peptides 1988;9:173–80; 3. Von Lueder et al. Pharmacol Ther 2014;144:41–9; 4. Packer et al. Circulation 2002;106:920–6; 5. McMurray et al. Eur J Heart Fail 2013;15:1062–73; 6. McMurray et al. N Engl J Med 2014;371:993–1004

Natriuretic peptides have potential beneficial actions in HF

Release of ANP and BNP from heart and CNP in vasculature[1,2]



- ⬇ Sympathetic outflow[1]
- ⬇ Vasopressin[1]
- ⬇ Salt appetite and water intake[1]

- ⬆ Na^+/H_2O loss[1]
- ⬇ Aldosterone[1]
- ⬇ Renin[1]

- ⬇ Hypertrophy[1,3–5,7]
- ⬇ Fibroblast proliferation[6–9]

Vasodilation[1,6,9]
- ⬇ Systemic vascular resistance[6]
- ⬇ Pulmonary artery pressure[6]
- ⬇ Pulmonary capillary wedge pressure[6]
- ⬇ Right atrial pressure[6]

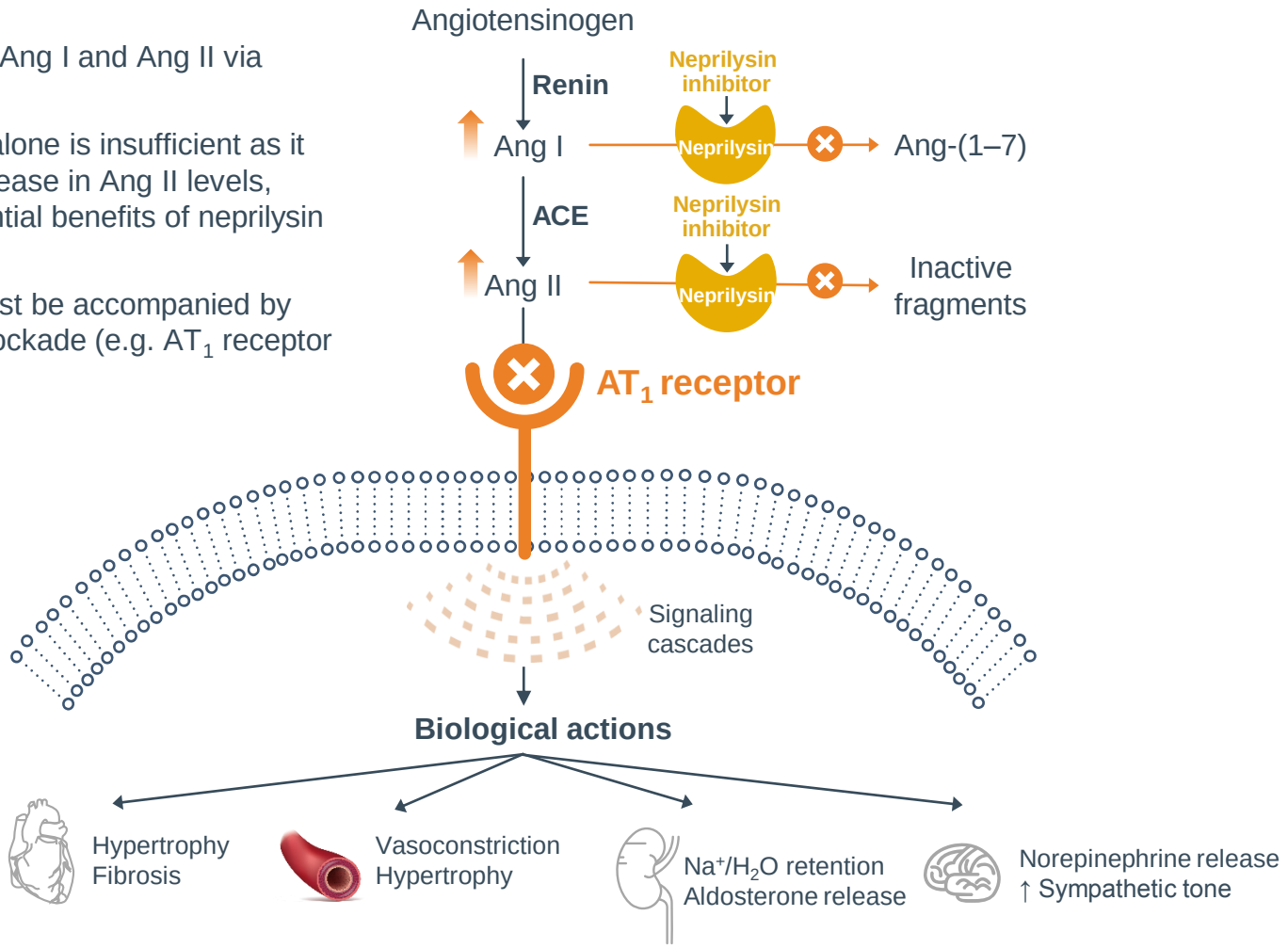
Neprilysin degrades natriuretic peptides and other substrates, including Ang II and vasoactive peptides relevant for cardiovascular physiology[10]

Ang II=angiotensin II; ANP=atrial natriuretic peptide; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide

1. Levin et al. N Engl J Med 1998;339:321–8; 2. Mangiafico et al. Eur Heart J 2013;34:886–93c; 3. Gardner et al. Hypertension 2007;49:419–26;
4. Tokudome et al. Circulation 2008;117;2329–39; 5. Horio et al. Hypertension 2000;35:19–24;
6. Langenickel and Dole. Drug Discov Today: Ther Strateg 2012; 9:e131–9; 7. D'Souza et al. Pharmacol Ther 2004;101:113–29;
8. Cao and Gardner. Hypertension 1995;25:227–34; 9. Lumsden et al. Curr Pharm Des 2010;16:4080–8; 10. Bayes-Genis et al. Curr Heart Fail Rep 2016;13:151–7

Neprilysin inhibition must be accompanied by simultaneous RAAS blockade

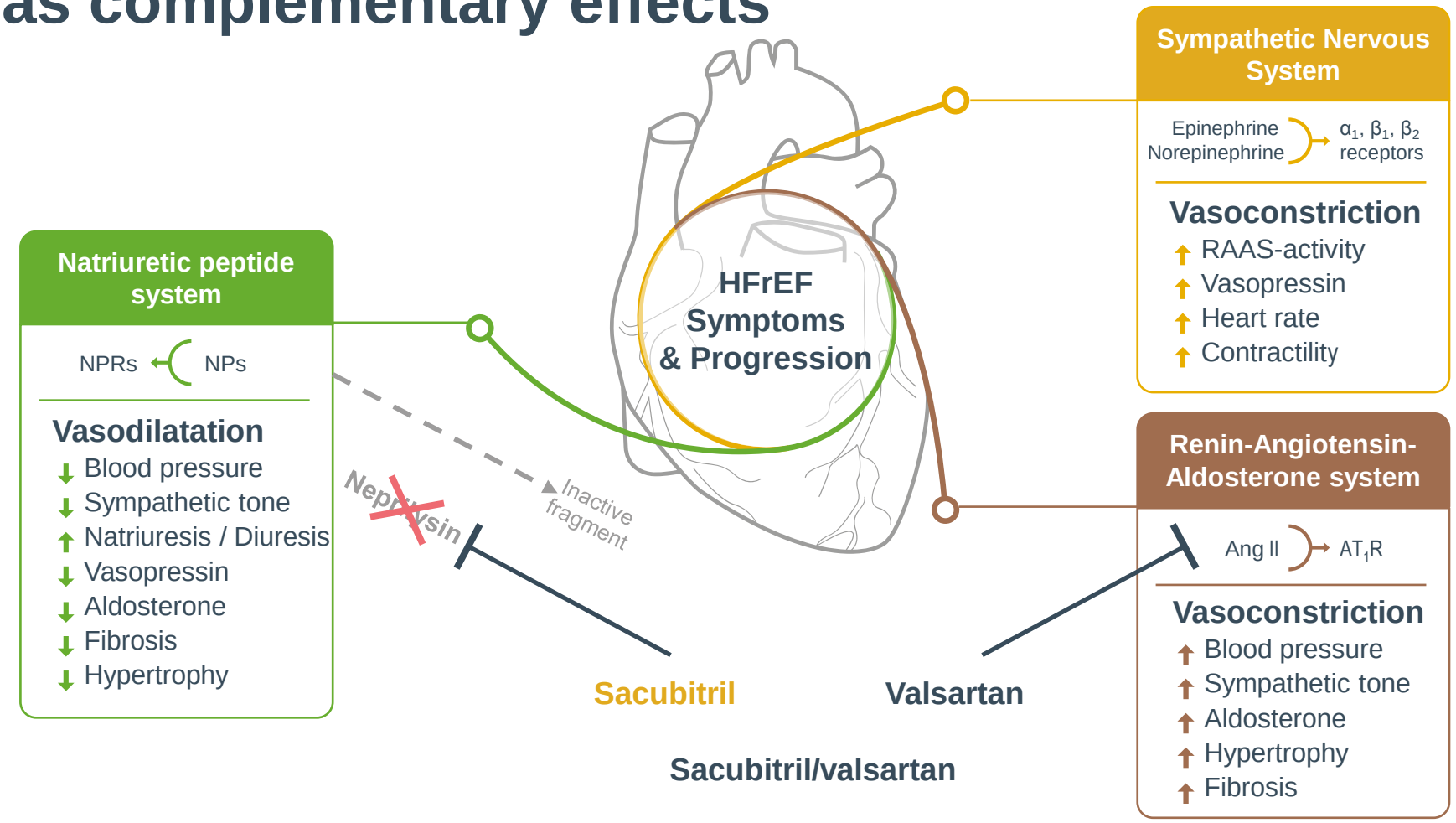
- Neprilysin metabolizes Ang I and Ang II via several pathways[1,2]
- Inhibition of neprilysin alone is insufficient as it associated with an increase in Ang II levels, counteracting the potential benefits of neprilysin inhibition[2]
- Neprilysin inhibition must be accompanied by simultaneous RAAS blockade (e.g. AT_1 receptor blockade)[2]



ACE=angiotensin-converting enzyme; AT_1=angiotensin II type 1; Ang=angiotensin; H_2O=water; Na=sodium; RAAS=renin-angiotensin- aldosterone system

1Von Lueder et al. Circ Heart Fail 2013;6:594–605; 2. Langenickel and Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9

Simultaneous inhibition of neprilysin and suppression of the RAAS with sacubitril/valsartan has complementary effects



AT_1R=angiotensin II type 1 receptor; RAAS=Renin-Angiotensin-Aldosterone-System; NPRs=natriuretic peptide receptors; NP=natriuretic peptide; SNS=sympathetic nervous system

1. Levin et al. N Engl J Med 1998;339:321–8; 2. McMurray et al. Eur J Heart Fail 2013;15:1062–73; 3. Nathisuwan and Talbert. Pharmacotherapy 2002;22:27–42; 4. Kemp and Conte. Cardiovasc Pathol 2012;21:365–71; 5. Schrier and Abraham. N Engl J Med 1999;341:577–85

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

Study design

PARADIGM-HF: key inclusion criteria

- Chronic HF NYHA FC II–IV with LVEF ≤40%*
- 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 lowered to ≤35% in a protocol amendment; #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: primary objective

- To evaluate the effect of LCZ 696 200 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]

Rationale for endpoint selection

- Primary outcome of CV death or HF hospitalization was chosen as the one that best reflects the major mortality and morbidity burden of HFrEF[1,2]
  - ~80% of deaths in recent trials in patients with HFrEF are CV related[3–5]
  - HF is associated with a high risk of hospitalization,[6] representing the leading cause of hospitalization in patients aged ≥65 years[6–9]
- The most commonly used primary endpoint in recent HF trials: CHARM-Added, SHIFT and EMPHASIS-HF[1]

ACE: angiotensin-converting enzyme; ACEI: angiotensin-converting-enzyme inhibitor; ARNI: angiotensin receptor neprilysin inhibitor; BID: twice daily; CHARM-Added: Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity in patients with HFrEF who were on ACE inhibitors; CV: cardiovascular; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure; HF: heart failure; 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; SHIFT: Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial

1. McMurray et al. Eur J Heart Fail 2013;15:1062–73; 2. Dunlay et al. Circ Cardiovasc Qual Outcomes 2011;4:68–75; 3. McMurray et al. Lancet 2003;362:767–77; 4. Swedberg et al. Lancet 2010;376:875–88; 5. Zannad et al. N Engl J Med 2011;364:11–2; 6. Cowie et al. Oxford Health policy Forum 2014; 7. Hunt et al. J Am Coll Cardiol 2009;53:e1–90; 8. Yancy et al. Circulation 2013;128:e240–327; 9. Rodriguez-Artalejo et al. Rev Esp Cardiol 2004;57:163–70

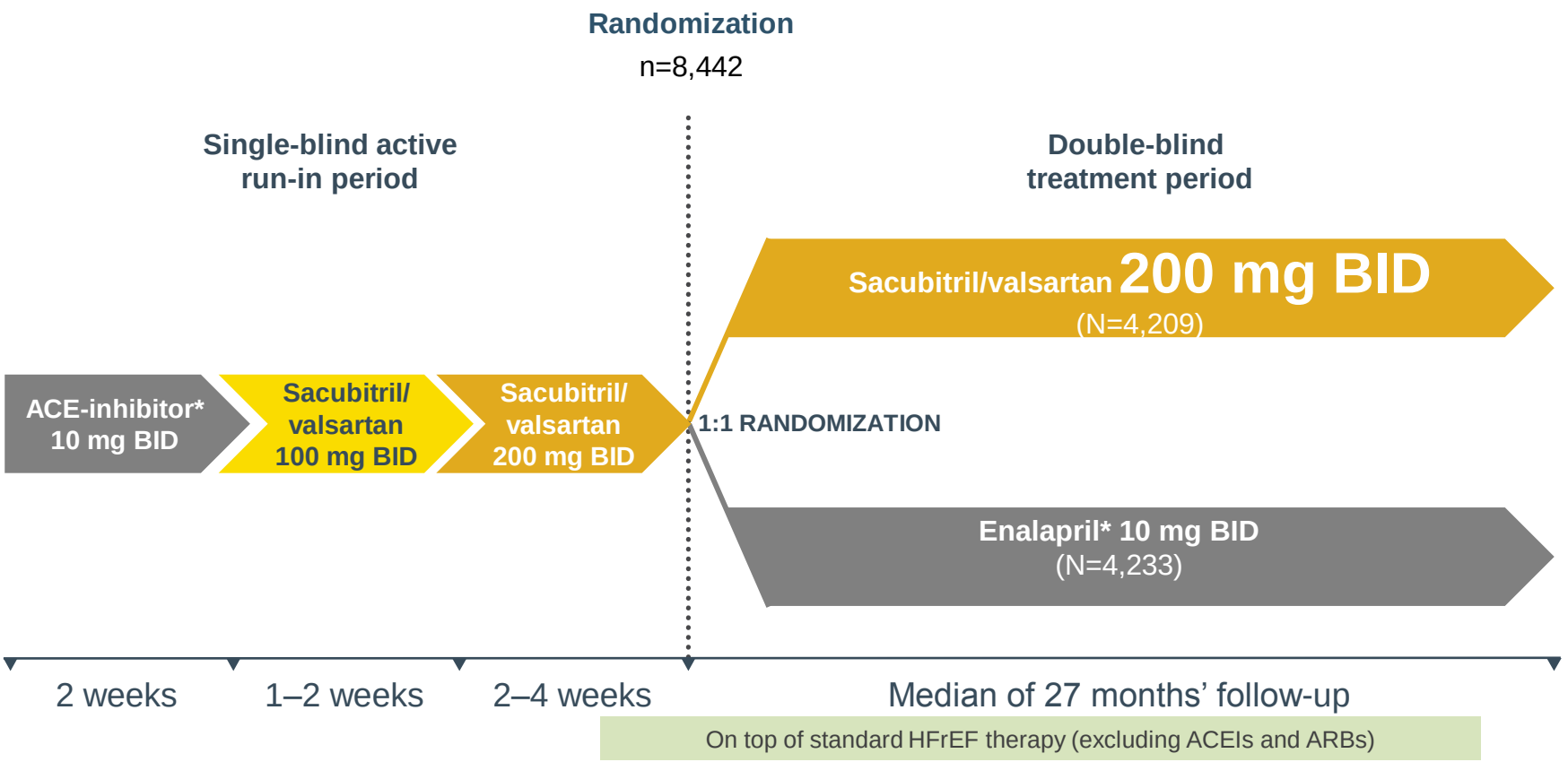
PARADIGM-HF: the most geographically diverse trial in patients with HFrEF

- 8,442 patients were randomized at 985 sites in 47 countries[1,2]

ACEI: angiotensin-converting-enzyme inhibitor; ARNI: angiotensin receptor neprilysin inhibitor; 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

1. McMurray et al. Eur J Heart Fail 2014;16:817–25; 2. McMurray et al. Eur J Heart Fail 2013;15:1062–73

PARADIGM-HF: study design



*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

ACEI: angiotensin-converting-enzyme inhibitor; *ARB:* angiotensin receptor blocker; *ARNI:* angiotensin receptor neprilysin inhibitor; *BID:* twice daily; *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; *TDD:* total daily dose

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;371:993–1004

Table 1. Characteristics of the Patients at Baseline.*

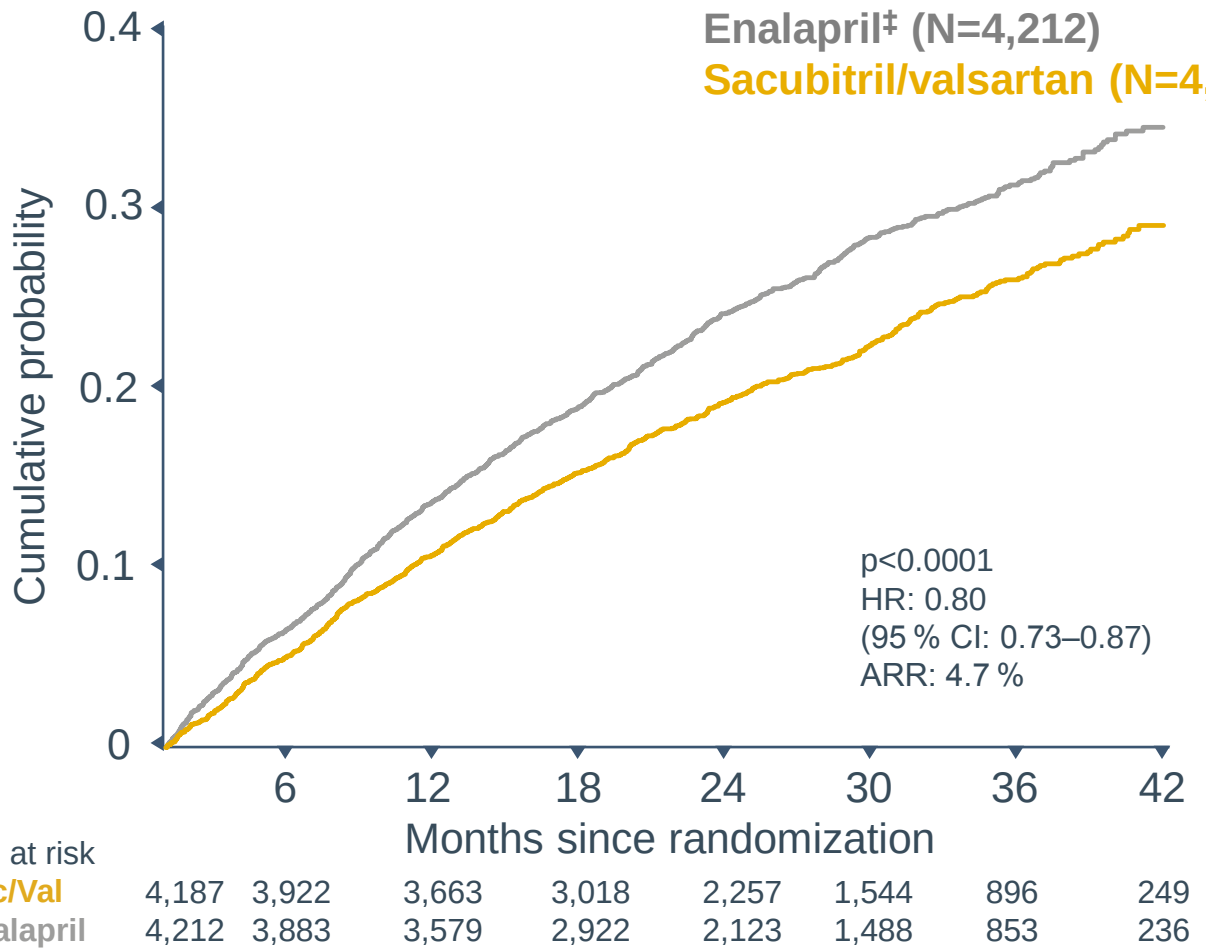
Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Age — yr	63.8±11.5	63.8±11.3
Female sex — no. (%)	879 (21.0)	953 (22.6)
Race or ethnic group — no. (%)†		
White	2763 (66.0)	2781 (66.0)
Black	213 (5.1)	215 (5.1)
Asian	759 (18.1)	750 (17.8)
Other	452 (10.8)	466 (11.1)
Region — no. (%)		
North America	310 (7.4)	292 (6.9)
Latin America	713 (17.0)	720 (17.1)
Western Europe and other‡	1026 (24.5)	1025 (24.3)
Central Europe	1393 (33.3)	1433 (34.0)
Asia–Pacific	745 (17.8)	742 (17.6)
Systolic blood pressure — mm Hg	122±15	121±15
Heart rate — beats/min	72±12	73±12
Body-mass index§	28.1±5.5	28.2±5.5
Serum creatinine — mg/dl	1.13±0.3	1.12±0.3
Clinical features of heart failure		
Ischemic cardiomyopathy — no. (%)	2506 (59.9)	2530 (60.1)
Left ventricular ejection fraction — %	29.6±6.1	29.4±6.3
Median B-type natriuretic peptide (IQR) — pg/ml	255 (155–474)	251 (153–465)
Median N-terminal pro–B-type natriuretic peptide (IQR) — pg/ml	1631 (885–3154)	1594 (886–3305)
NYHA functional class — no. (%)¶		
I	180 (4.3)	209 (5.0)
II	2998 (71.6)	2921 (69.3)
III	969 (23.1)	1049 (24.9)
IV	33 (0.8)	27 (0.6)
Missing data	7 (0.2)	6 (0.1)

Well-treated population in PARADIGM-HF

Table 1. (Continued.)

Characteristic	LCZ696 (N = 4187)	Enalapril (N = 4212)
Treatments at randomization — no. (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	623 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)

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



NNT 21§

20%

RELATIVE RISK REDUCTION OF PRIMARY ENDPOINT

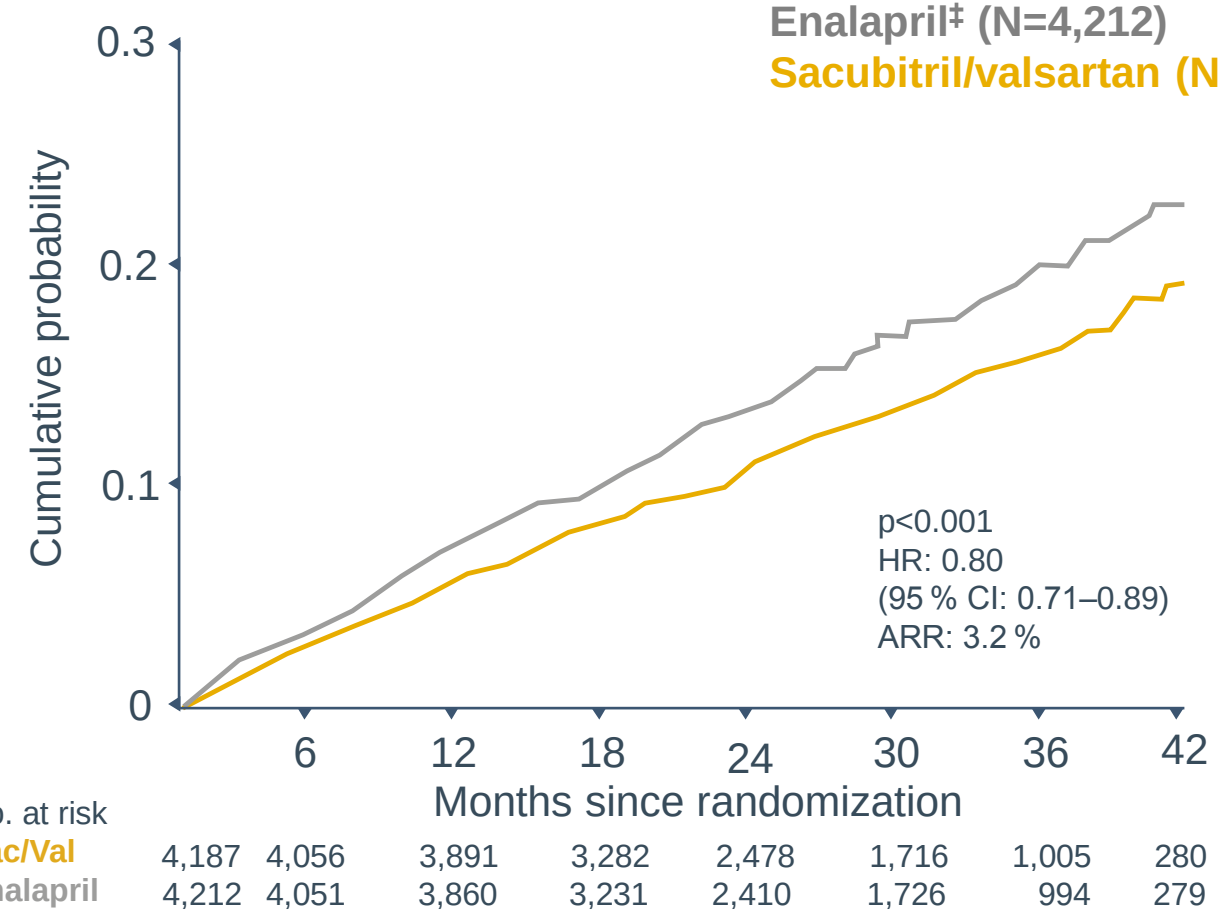
No. at risk								
Sac/Val	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

*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

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

Sacubitril/valsartan significantly reduced CV mortality*



NNT 32 §

20%

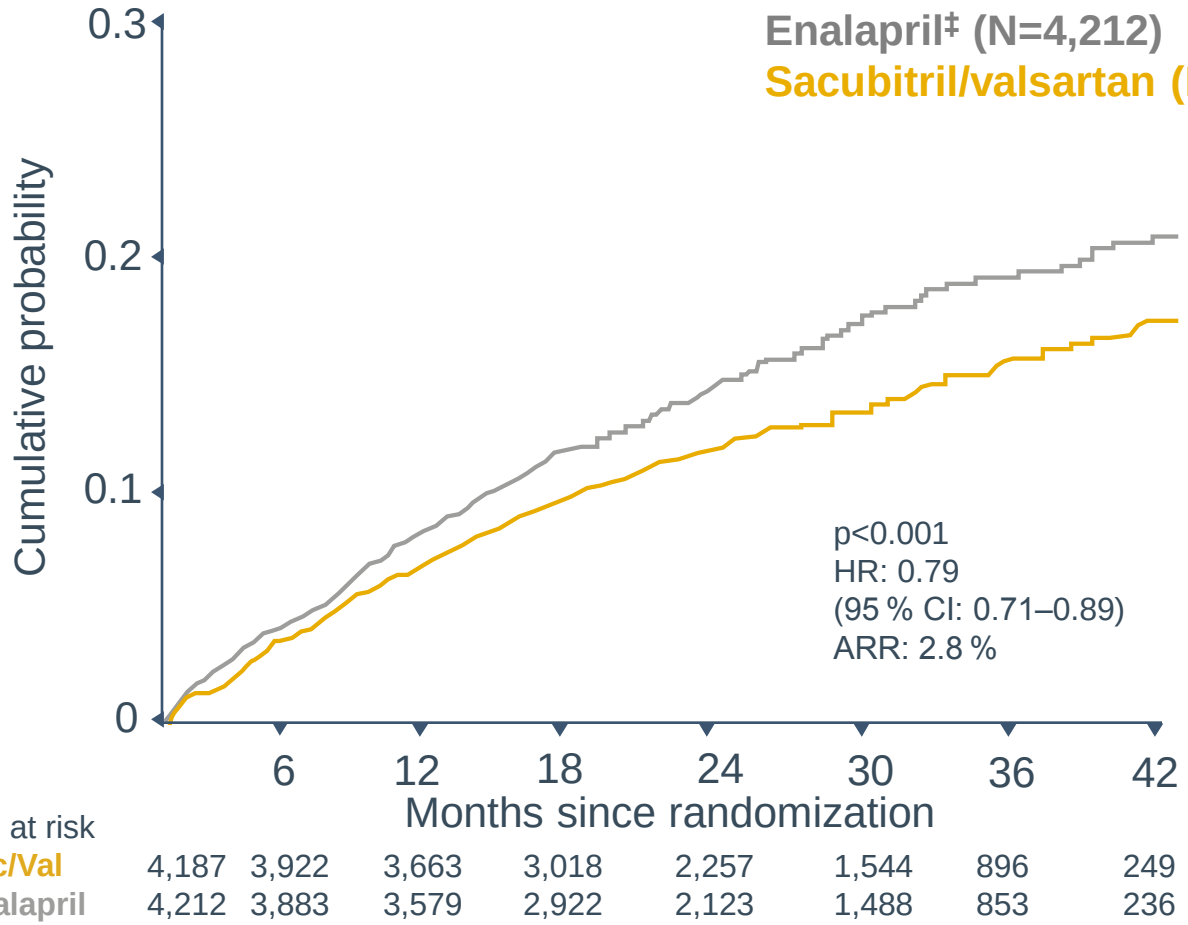
RELATIVE RISK REDUCTION OF CARDIOVASCULAR MORTALITY

*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

Sacubitril/valsartan significantly reduces the risk of first HF hospitalization, keeping HFrEF patients out of the hospital*



NNT 36§

21%

RELATIVE RISK REDUCTION OF FIRST HOSPITALIZATION FOR HF

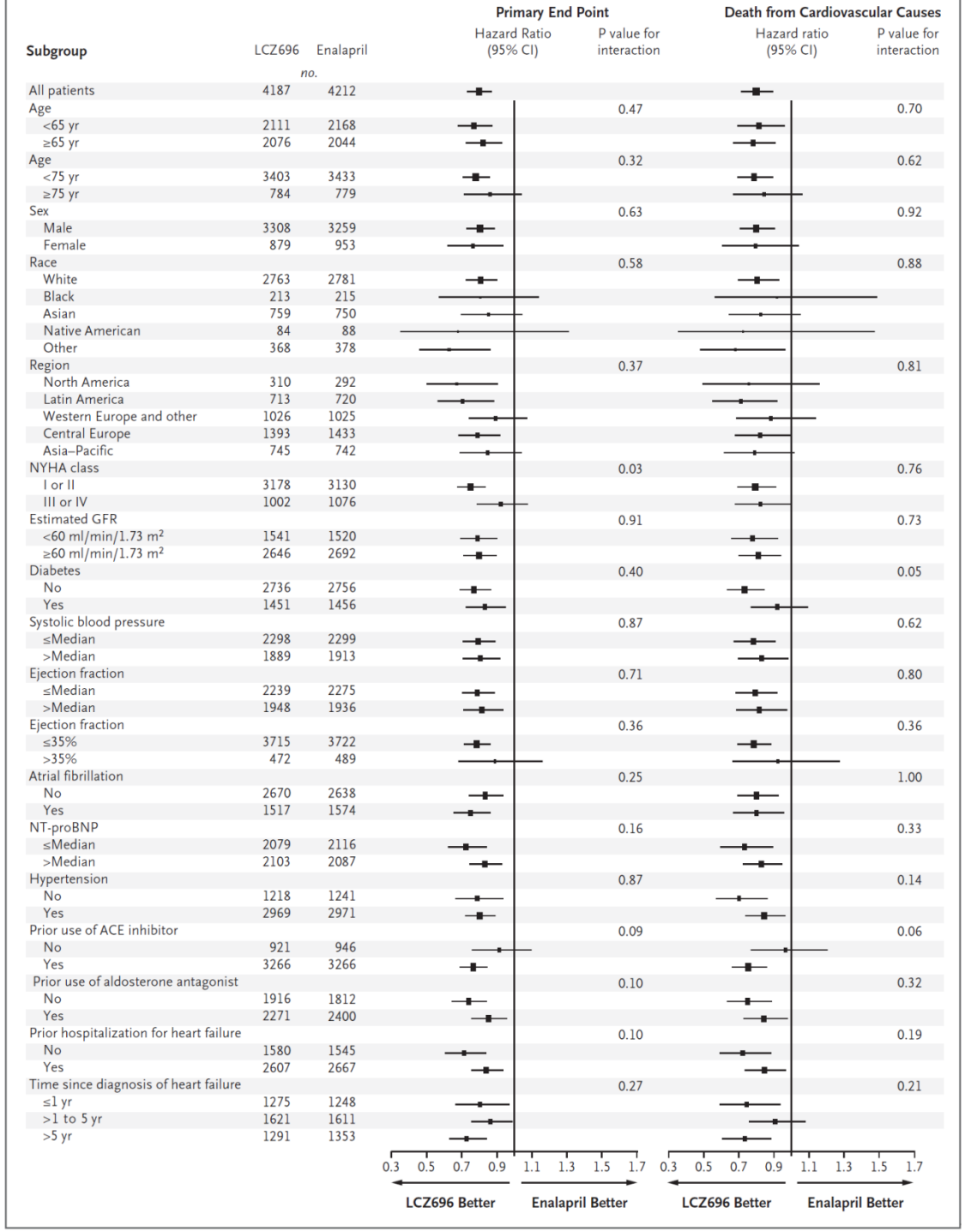
*Compared with enalapril, as assessed via time to first hospitalization for HF (single component of primary endpoint). ‡Enalapril 10 mg 2x daily as comparator vs sacubitril/valsartan 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy). §27 months since randomization (median)

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

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

Subgroup data

- NYHA III/IV (x)
- LVEF >35% (x)
- Non-white (x)
- Age >=75 (x)
- Prior use of ACEI (x)



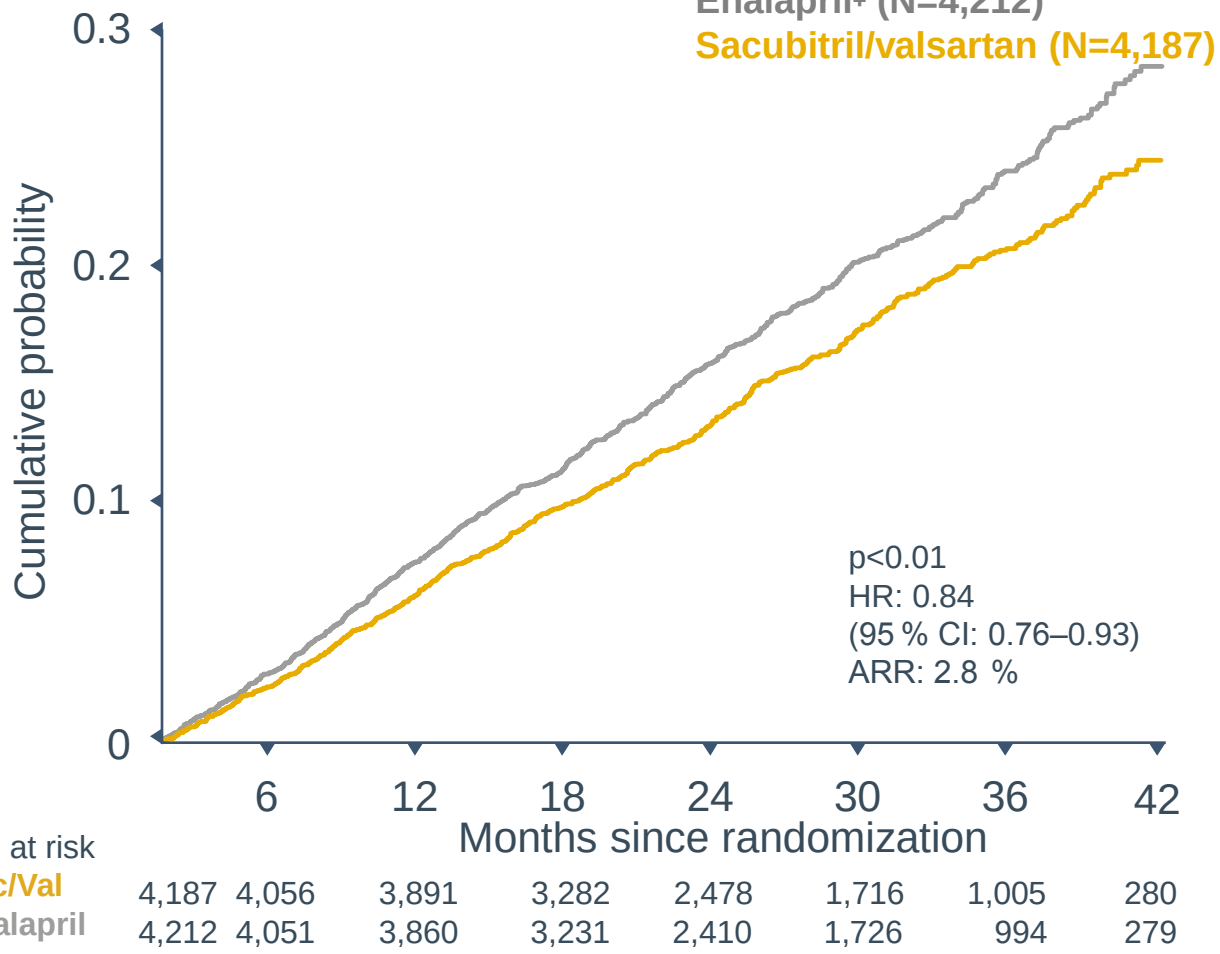
Secondary outcomes – summary

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 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

Sacubitril/valsartan significantly reduced all-cause mortality*



NNT 36 §

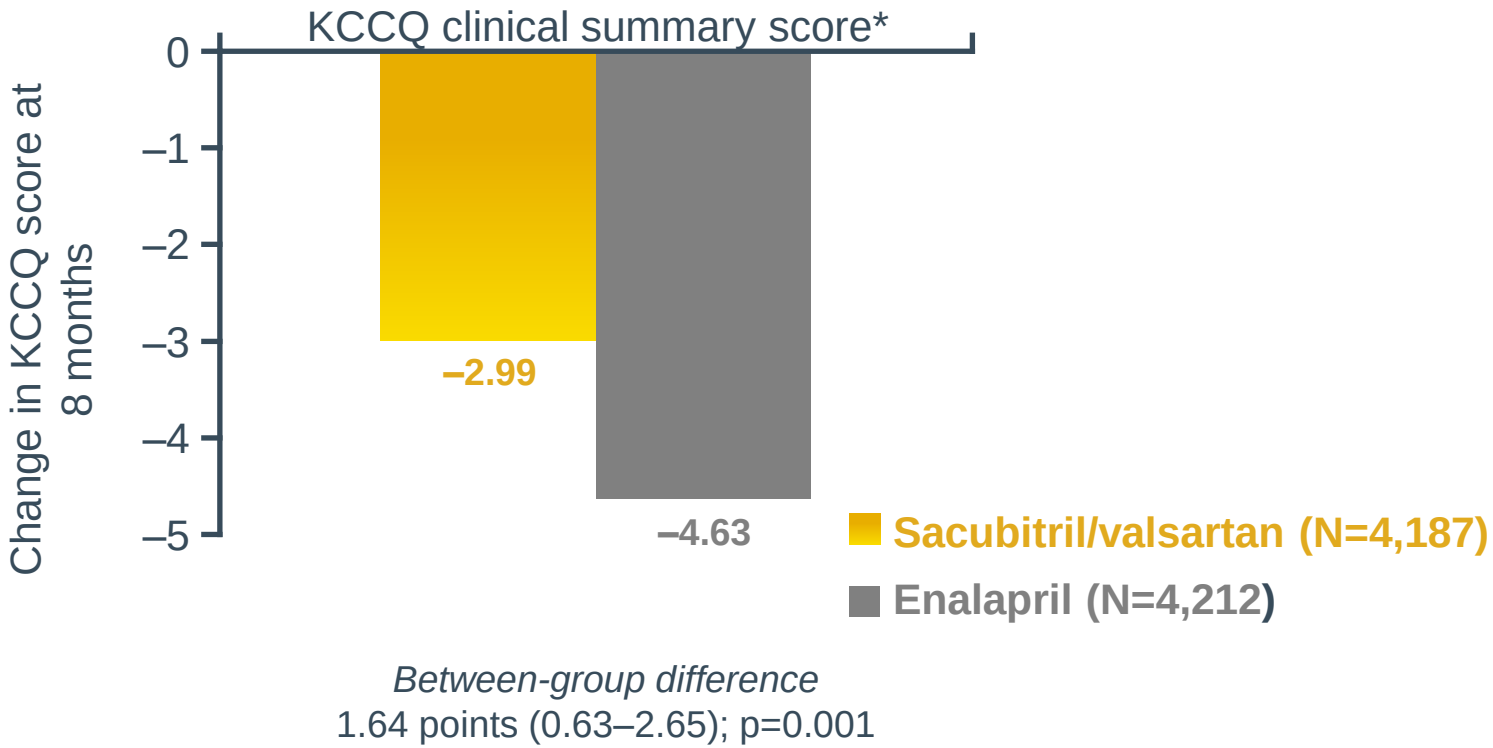
16%

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

Mean change from baseline to Month 8 in KCCQ clinical summary score was lower in the sacubitril/valsartan group than in the enalapril group



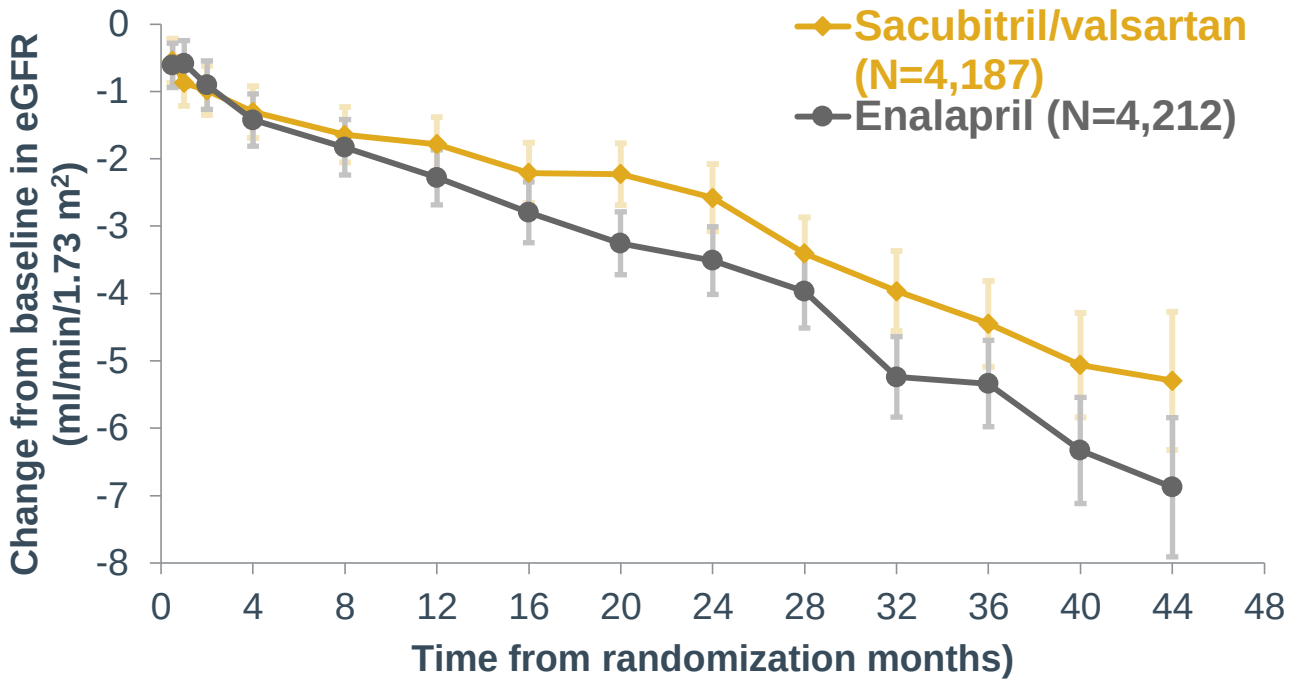
Between-group difference
1.64 points (0.63–2.65); p=0.001

*The treatment effect is the least-squares mean (±SE) of the between-group difference

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

No significant difference in progression of renal dysfunction with sacubitril/valsartan, compared with enalapril

Change from baseline in eGFR

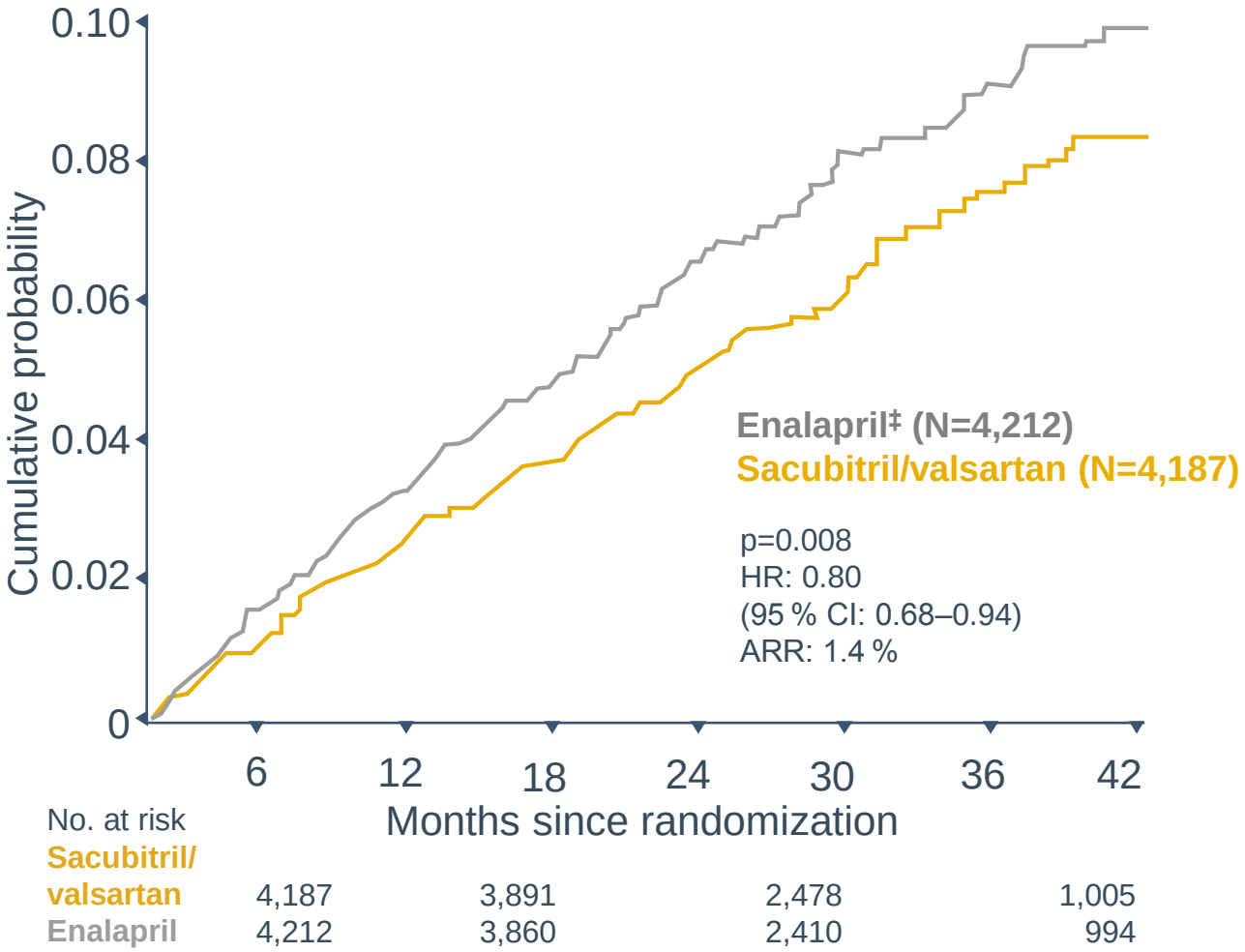


Change in eGFR –6.1 mL/min/1.73 m^2 over 44 months (sacubitril/valsartan –5.4 ± 1.0 vs enalapril –6.8 ± 1.0 mL/min/1.73 m^2)
Slope eGFR: sacubitril/valsartan –1.14 vs enalapril –1.53 mL/min/1.73 m^2/year (p=0.0047)

eGFR=estimated glomerular filtration rate

Gamman et al. Oral presentation at the ESC congress 2015, London, UK, 29 August – 2 September 2015

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



20%

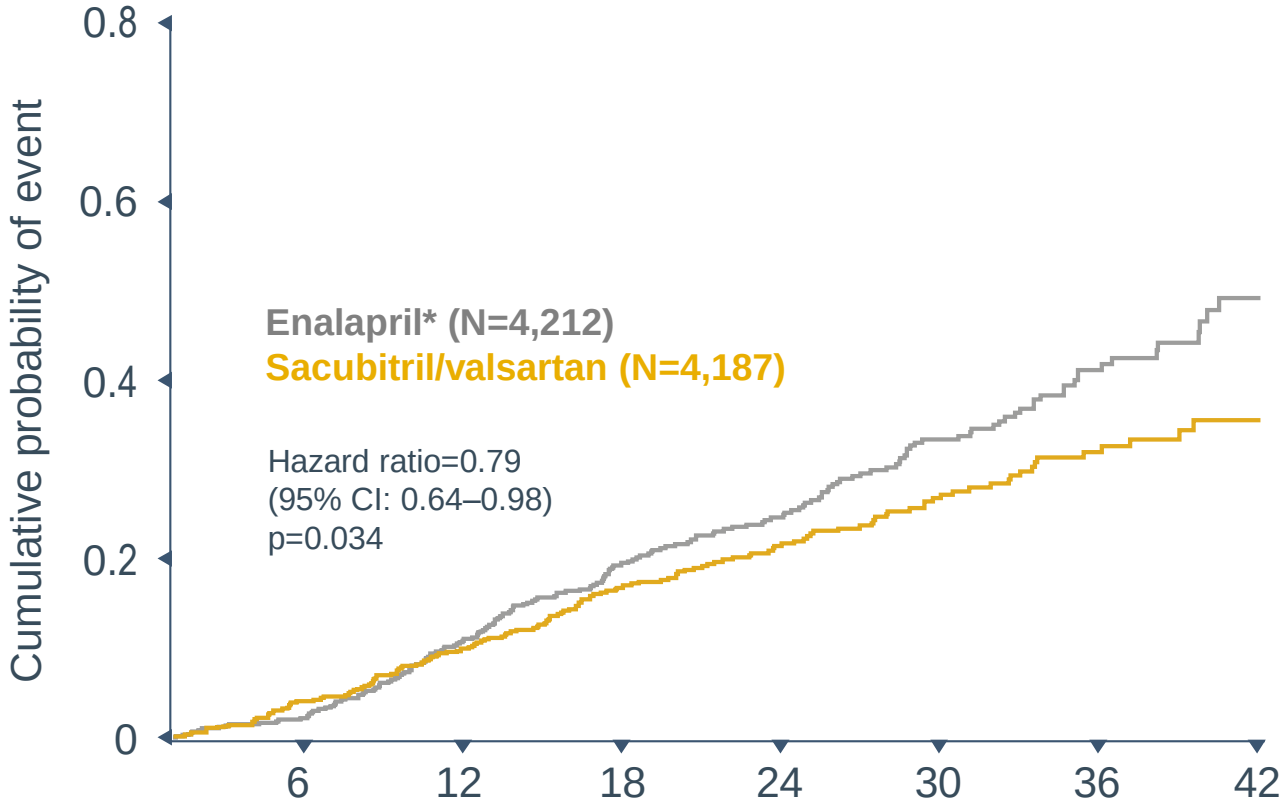
RELATIVE RISK REDUCTION OF SUDDEN DEATH

*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

Entresto™ sacubitril/valsartan

Death due to worsening of heart failure was significantly reduced by Sacubitril/valsartan treatment, compared with enalapril



No. at risk				
Sacubitril/valsartan	4,187	3,891	2,478	1,005
Enalapril	4,212	3,860	2,410	994

21%

RELATIVE RISK REDUCTION
OF Death due to worsening of HF

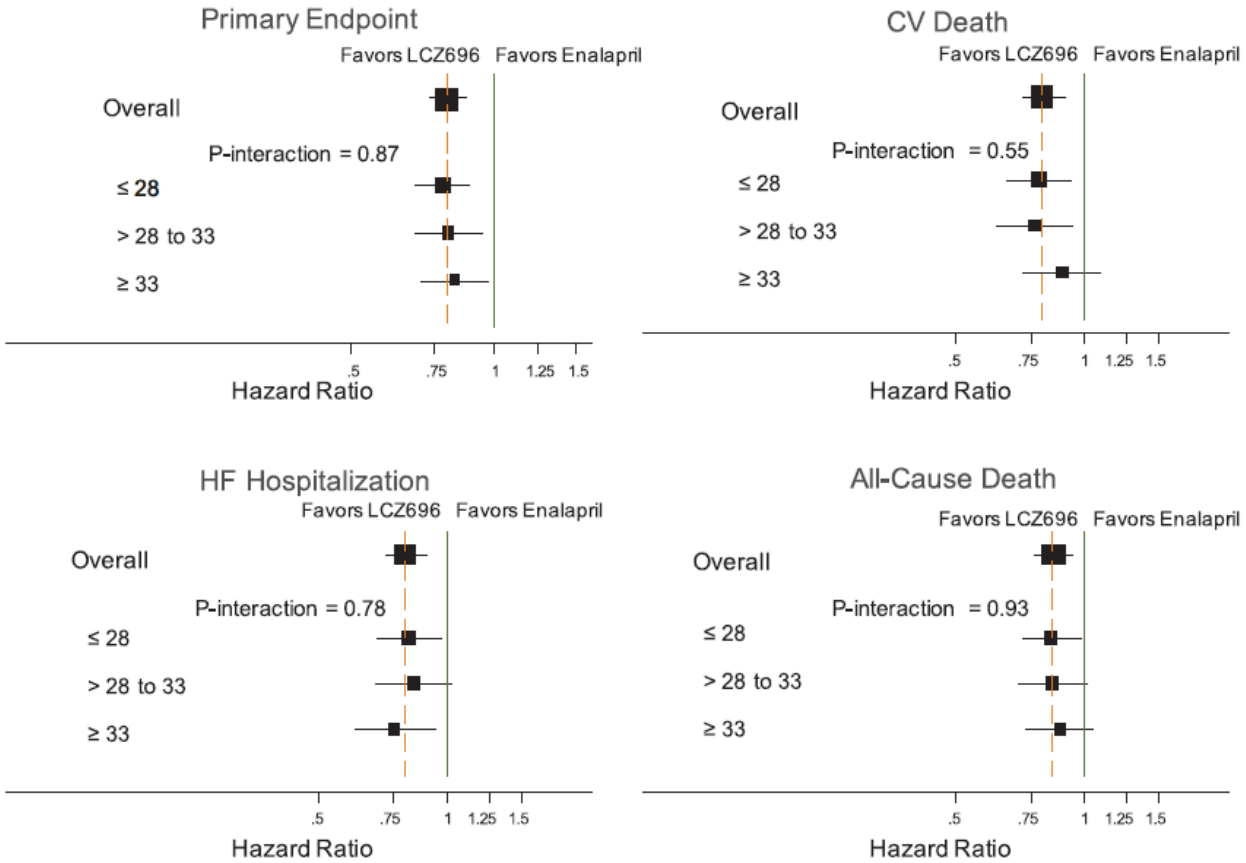
*Enalapril 10 mg 2x daily as comparator vs sacubitril/valsartan 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy). CI=confidence interval

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

Entresto™ sacubitril/valsartan

TW1804808478

Treatment Effect of Sacubitril/valsartan are consistent by Tertile of LVEF for All Outcomes



Entresto as effective at reducing cardiovascular death and HF hospitalization throughout the LVEF spectrum.

Solomon SD, Claggett B, Desai AS, Packer M, Zile M, Swedberg K, Rouleau JL, Shi VC, Starling RC, Kozan Ö, Dukat A, Lefkowitz MP, McMurray JJ et al., Circ Heart Fail. 2016 Mar;9(3):e002744. doi: 10.1161/CIRCHEARTFAILURE.115.002744.

Sacubitril/valsartan safety

Table 3. Adverse Events during Randomized Treatment.*

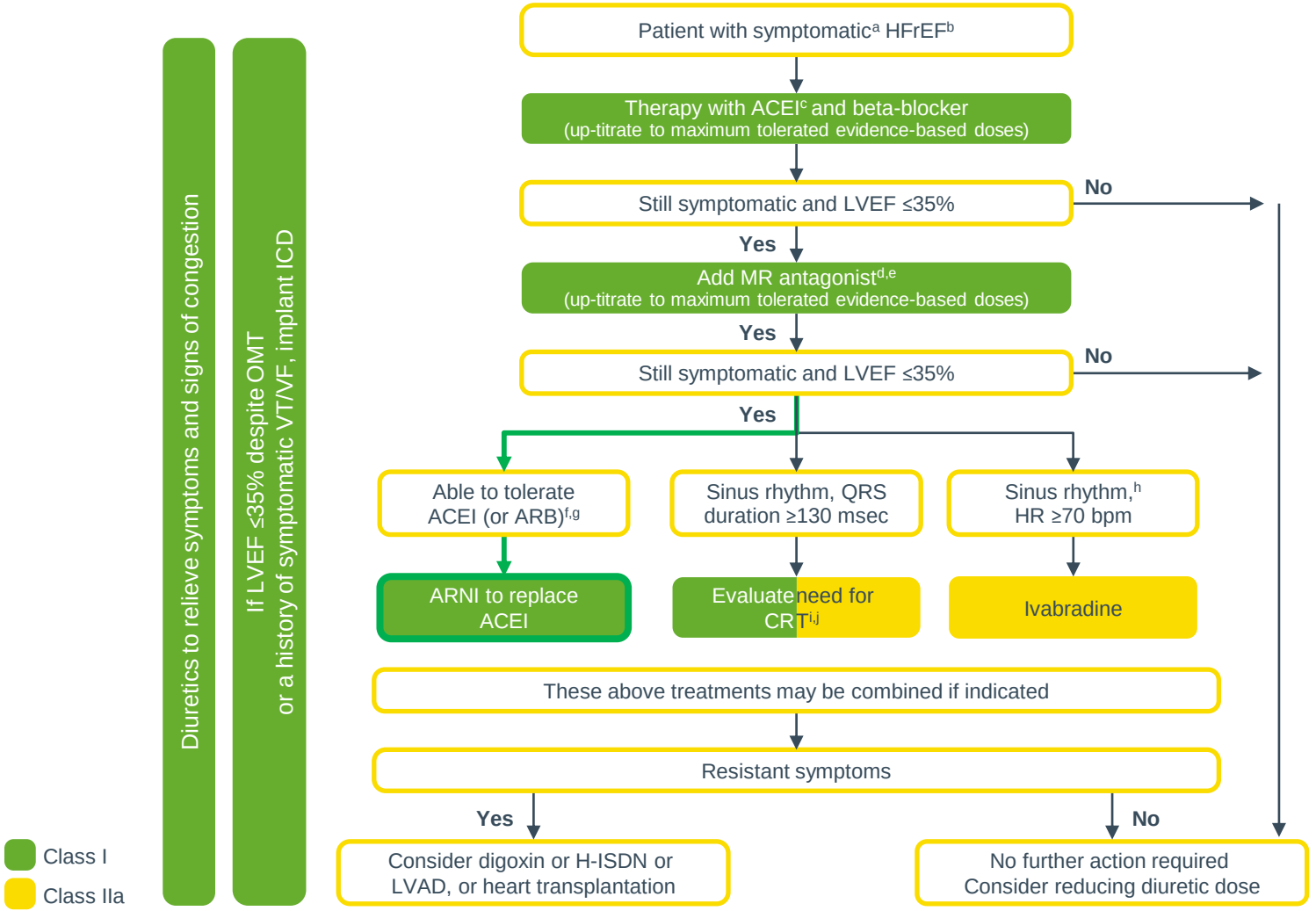
Event	LCZ696 (N = 4187)	Enalapril (N = 4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated 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	—

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

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

2016 ESC Guidelines	Class	Level
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.	I	B

2016 ESC guideline recommendations for the treatment of patients with symptomatic HFrEF



Green indicates a class I recommendation; yellow indicates a class IIa recommendation.

a. Symptomatic = NYHA Class II–IV; b. HFrEF = LVEF <40%; c. If ACE inhibitor not tolerated/contra-indicated, use ARB; d. If MR antagonist not tolerated/contra-indicated, use ARB; e. With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP > 250 pg/mL or NTproBNP > 500 pg/mL in men and 750 pg/mL in women); f. With an elevated plasma natriuretic peptide level (BNP ≥ 150 pg/mL or plasma NT-proBNP ≥ 600 pg/mL, or if HF hospitalization within recent 12 months plasma BNP ≥ 100 pg/mL or plasma NT-proBNP ≥ 400 pg/mL); g. In doses equivalent to enalapril 10 mg b.i.d; h. With a hospital admission for HF within the previous year; i. CRT is recommended if QRS ≥ 130 msec and LBBB (in sinus rhythm); j. CRT should/may be considered if QRS ≥ 130 msec with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular capture in place (individualised decision)

Ponikowski et al. Eur Heart J 2016;37:2129–200

Entresto™ sacubitril/valsartan

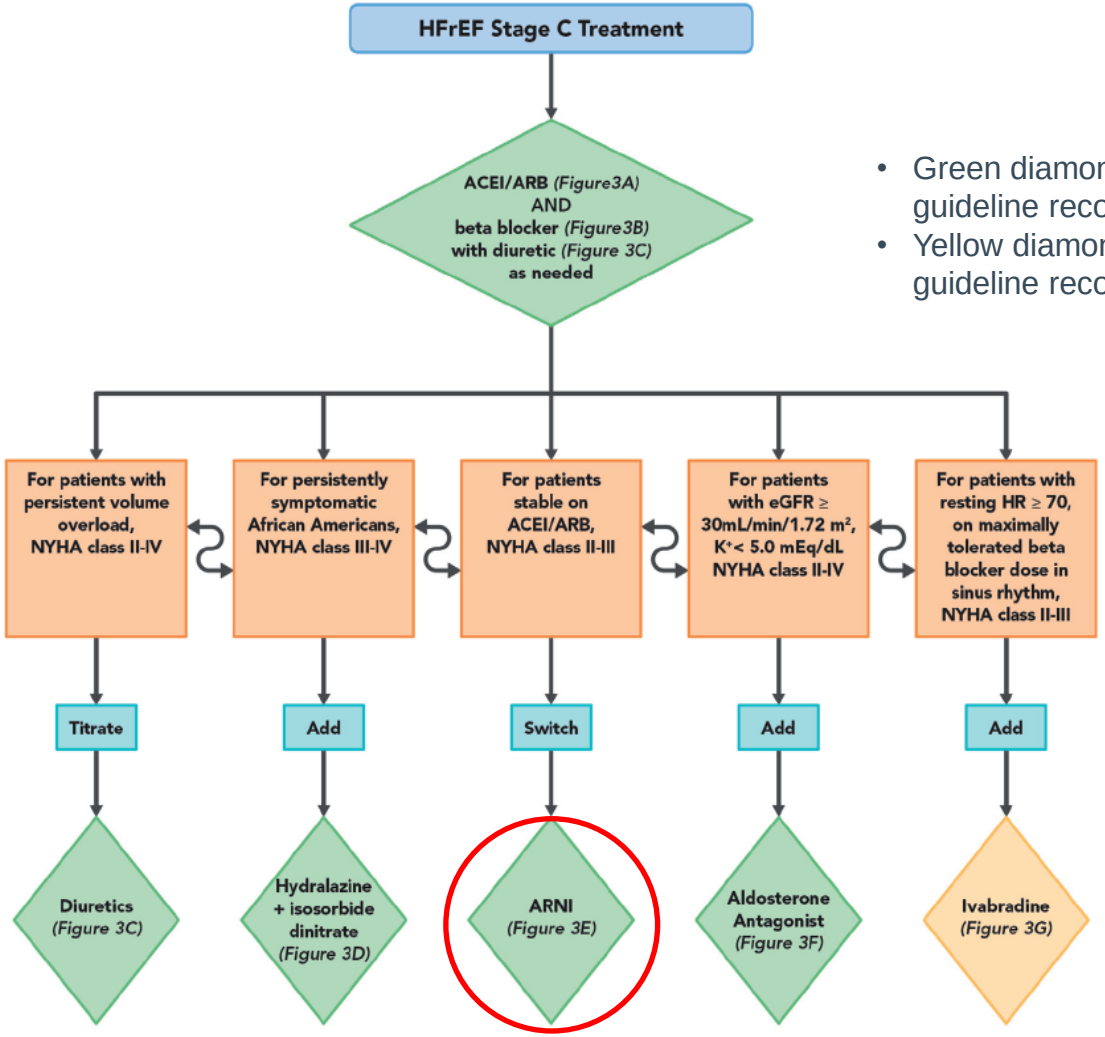
TW1804808478

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

ACC/AHA 2017 Guidelines	Class	Level
Recommend sacubitril/valsartan OR ACE inhibitors OR ARBs for patients with HFrEF to reduce morbidity and mortality.	I	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.	I	B-R

Circulation 2017;136:e137–e161

Treatment Algorithm for Guideline-Directed Medical Therapy Including Novel Therapies



- Green diamonds indicate Class I guideline recommendations
- Yellow diamond indicates a Class II guideline recommendation.

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitor; eGFR: estimated glomerular filtration rate; HFrEF: heart failure with reduced ejection fraction; HR: heart rate; NYHA: New York Heart Association.

2017 ACC Expert Consensus

Summary : PARADIGM-HF series

In PARADIGM-HF study, **Majority of Patients were in NYHA class II** and were on stable HF medication at baseline

Sacubitril/valsartan significantly reduced CV mortality or first HF hospitalization compared with enalapril (20%)

Sacubitril/valsartan significantly reduced all-cause mortality compared with enalapril (16%)

Sacubitril/valsartan to replace ACEI or ARB in persistent symptomatic HFrEF patients (AHA, ESC guideline)

Sacubitril/valsartan is first line therapy in AHA guideline


THE
REAL
WORLD

ARNI in real world

- Early insights into the characteristics and evolution of clinical parameters in a cohort of patients prescribed sacubitril/valsartan in Germany
- Early real-world implementation of sacubitril/valsartan in Sweden (conference data)
- Sacubitril/valsartan initiation among renin-angiotensin aldosterone system inhibitor-naïve heart failure patients with reduced ejection fraction-USA (conference data)

CM Franchise

Early insights into the characteristics and evolution of clinical parameters in a cohort of patients prescribed sacubitril/valsartan in Germany

Wachter R, et al.

Postgrad Med. 2018 Apr;130(3):308-316
(https://doi.org/10.1080/00325481.2018.1442090)

NOVARTIS

German RWE: Study objectives

- Provide early insights into sacubitril/valsartan (sac/val) prescription patterns and the demographic and clinical characteristics of patients prescribed sac/val in primary care and cardiology settings in Germany.
- Patient demographics and clinical characteristics were also compared with those of patients from the PARADIGM-HF trial.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure; sac/val, sacubitril/valsartan

Wachter R, et al. Postgrad Med. 2018; DOI: 10.1080/00325481.2018.1442090

German RWE: Methods and data analysis (1/2)

Study design

- Retrospective cohort study
- Inclusion criteria: patients with HF and aged ≥18 years
- Study period: January 1st –December 31st 2016
- Look-back period* January 1st 1992

Data source

- German IMS® disease analyzer electronic medical records database
- Data derived from PCPs and cardiologist practices (panels)

Study population

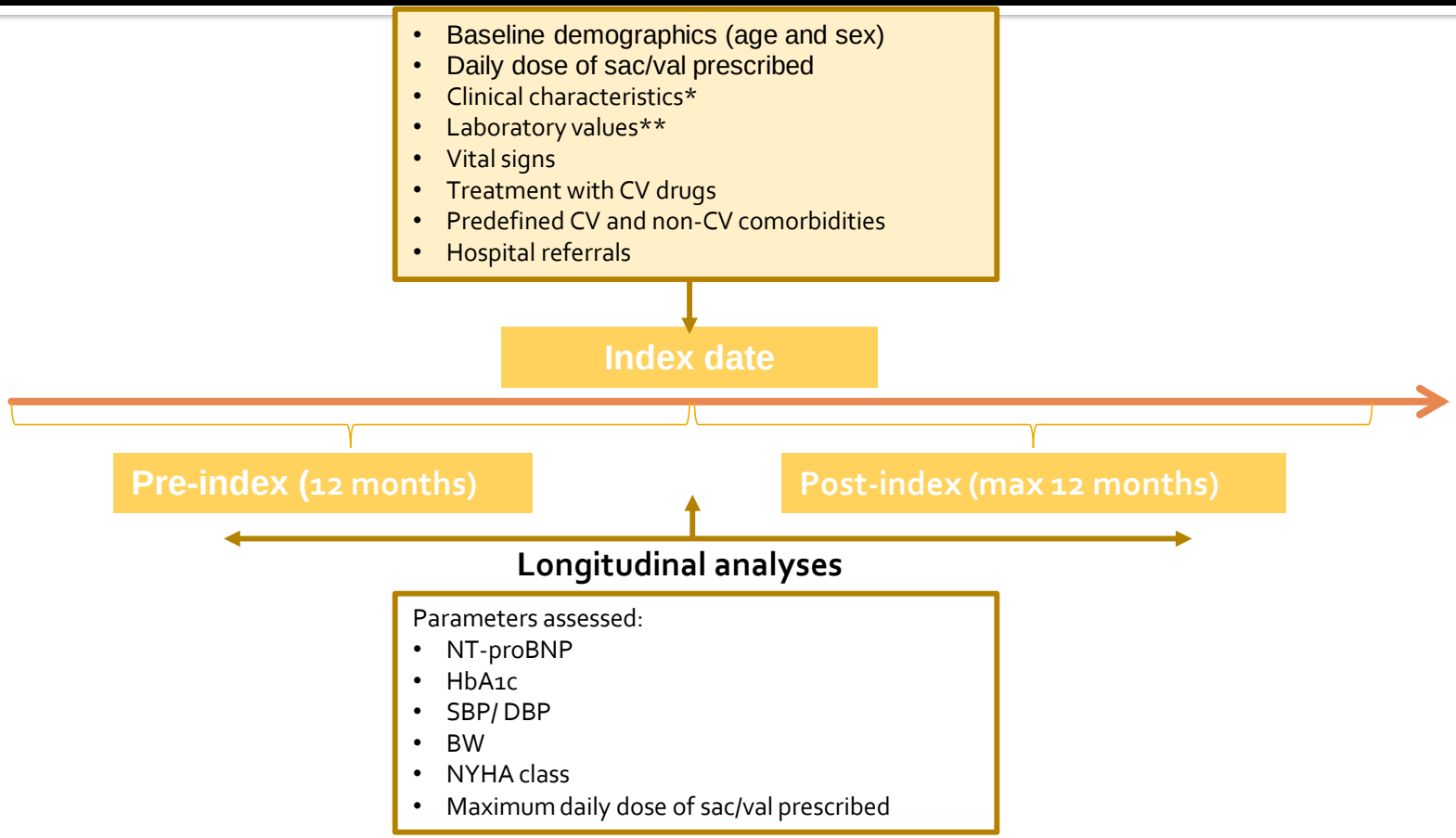
- The study population was divided into 2 cohorts:
  - Sac/val¶ (n = 1643)
  - pHF-SoC (reference cohort)# (n = 25,264)

*At any time in the full history of the database.
¶ Patients who received ≥1 prescription for sac/val during the study period (n=1643). The date of the first sac/val prescription defined the index date for this cohort.
#Patients with prevalent HF who received the minimum standard of care for patients with HFrEF NYHA class II–IV. These patients had to have ≥1 diagnosis of HF during the study period and ≥1 additional diagnosis of HF (according to ICD-10 codes) during the look-back period* (n = 25,264). In addition, ≥1 prescription for an ACEI or ARB and a BB during the study period, without a prescription for sac/val was also needed. The date of the first HF diagnosis in the study period defined the index (the date of the first HF diagnosis in the study period) for this cohort.

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; EMR, electronic medical record; HF, heart failure; HFrEF, heart failure reduced ejection fraction; NYHA, New York Heart Association; PARADIGM-HF, prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure; PCP, primary care practice; pHF-SoC, prevalent heart failure standard of care; sac/val, sacubitril/valsartan

Wachter R, et al. Postgrad Med. 2018; DOI: 10.1080/00325481.2018.14420 90

German RWE: Methods and data analysis (2/2)



*Clinical characteristics (LVEF, NYHA class, BMI, body weight) ** laboratory values (NT-proBNP, eGFR, urea, hemoglobin, HbA1c, CRP, SBP, DBP). Data were analyzed from a subset of patients prescribed sac/val who had ≥1 measurement of the same clinical parameter during the 12 months pre-index (or on the index date) and the 12 months post-index. Linear mixed-effects models were used to estimate changes in these parameters

BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain 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; SBP, systolic blood pressure; sac/val, sacubitril/valsartan

Wachter R, et al. Postgrad Med. 2018; DOI: 10.1080/00325481.2018.1442090

German RWE: Baseline and clinical characteristics (1/3)

- Male patients were more prevalent in the sac/val cohort than in the pHF-SoC cohort. The proportion of male patients in the sac/val Cards cohort was similar to that in the PARADIGM-HF study (79%).[1]
- Overall, patients treated by cardiologists were younger in both the cohorts and more closely resembled those enrolled in PARADIGM-HF (63.8 ± 11.5 years), and were more frequently male than those from the PCP panel.[1]

	PARADIGM-HF study[a]	Real-world study					
		PCP panel			Cardiologist panel		
	N = 4187	**Sac/val cohort N = 1041**	pHF-soC cohort N = 24,513	p-value Sac/val vs pHF-SoC	**Sac/val cohort N = 602**	pHF-SoC cohort N = 1111	p-value Sac/val vs pHF-SoC
Male, n (%)*	3308 (79.0)	**700 (67.0)**	11,745 (49.0)	<0.001	**459 (76.0)**	738 (66.0)	<0.001
Age, years Mean (SD)	63.8 (11.4)	**73.1 (12.2)**	76 (11.3)	<0.001	**68.9 (11.7)**	68.7 (11.6)	0.7047
BMI, kg/m²							
Mean (SD)	28.2 (5.5)	**30 (6.2) n = 233**	30.7 (6.1) n = 5067	0.1137	**28.9 (6.1) n = 143**	29.1 (5.1) n = 254	0.7941
HbA1c							
Mean (SD)	-	**6.7 (1.2) n = 417**	6.5 (1.0) n = 9306	0.5674	**6.7 (1.2) n = 36**	6.1 (0.7) n = 72	0.0431

[a]In the PARADIGM-HF study, all characteristics presented were assessed in the run-in period before sac/val initiation[2]
p values for HbA1c (PCP panel) are derived from a Wilcoxon–Mann–Whitney test. All other p values are derived from the Student's t-test;
*n (%) indicates the number of patients for whom data are available.

BMI, body mass index; HbA1c, glycated haemoglobin; NR, not reported; NYHA, New York Heart Association; PCP, primary care practitioner; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; pHF-SoC, prevalent heart failure standard of care; sac/val, sacubitril/valsartan; SD, standard deviation

1. Wachter R, et al. Postgrad Med. 2018; DOI: 10.1080/00325481.2018.1442090
2. McMurray JJ, et al. N Engl J Med. 2014;371:993–1004

German RWE: Baseline and clinical characteristics (2/3)

- Overall, patients prescribed sac/val had a greater severity of HF symptoms (>50% in NYHA class III/IV) than the pHF-SoC cohort, and than patients enrolled in PARADIGM-HF (72% in NYHA Class II).[1]
- NT-proBNP levels were also higher in the sac/val cohort than in the pHF-SoC cohort and in PARADIGM-HF.[1]

	PARADIGM-HF study[a]	Real-world study					
		PCP panel			Cardiologist panel		
	N = 4187	**Sac/val cohort N = 1041**	pHF-SoC cohort N = 24,513	p sac/val vs pHF-SoC	**Sac/val cohort N = 602**	pHF-SoC cohort N = 1111	p sac/val vs pHF-SoC
	-						
NYHA class		n = 168	n = 3415		n = 113	n = 359	
n (%) **I**	180 (4.3)	**5 (3)**	284 (8)	<0.001	**1 (1)**	24 (7)	<0.001
II	2998 (71.6)	**42 (25)**	1305 (38)		**37 (33)**	200 (56)	
III	969 (23.1)	**95 (57)**	1471 (43)		**65 (58)**	119 (33)	
IV	33 (0.8)	**26 (15)**	355 (10)		**10 (9)**	16 (4)	
NT-proBNP, pg/mL							
Median (IQR)	1631 (885–3154) n = 4187	**2100 (1018–4708) n = 200**	1093 (387–2355) n = 999	<0.001	**2372 (697–3388) n = 25**	553 (335–1846) n = 11	0.0224

[a]In the PARADIGM-HF study, all characteristics presented were assessed in the run-in period before sac/val initiation[2]
p values for HbA1c (PCP panel) are derived from a Wilcoxon–Mann–Whitney test. All other p values are derived from the Student's t-test;
n, indicates the number of patients for whom data are available.

IQR, interquartile range; NYHA, New York Heart Association; NR, not reported; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PARADIGM-HF, prospective comparison of ARNI with an angiotensin-converting enzyme inhibitor to determine impact on global mortality and morbidity in heart failure; PCP, primary care practitioner; pHF-SoC, patients with prevalent heart failure receiving the standard of care (for patients with HFrEF NYHA class II–IV); sac/val, sacubitril/valsartan; SD, standard deviation

1. Wachter R, et al. Postgrad Med. 2018; DOI: 10.1080/00325481.2018.1442090
2. McMurray JJ, et al. N Engl J Med. 2014;371:993–1004

German RWE: Baseline and clinical characteristics (3/3)

- A greater proportion of patients in the sal/val cohort had an eGFR indicative of stage ≥3 CKD. In the PARADIGM-HF trial, most patients had an eGFR indicative of stage 2–3 CKD disease.[1]
- SBP was lower in the sac/val than in the pHF-SOC cohort and was similar to baseline SBP (~122 mm Hg) of patients enrolled in PARADIGM-HF.[1,2]

	PARADIGM-HF study[a]	Real-world study					
		PCP panel			Cardiologist panel		
		Sac/val cohort N = 1041	pHF-soC cohort N = 24,513	p sac/val vs pHF-SoC	**Sac/val cohort N = 602**	pHF-SoC cohort N = 1111	p sac/val vs pHF-SoC
eGFR, mL/min/1.73 m²							
		n = 563	n = 13,175		**n = 515**	n = 956	
>90 (stage 1)	NR	**47 (8.0)**	1564 (12.0)		**10 (11.0)**	29 (19.0)	
60–90 (stage 2)	NR	**201 (36.0)**	5400 (41.0)		**36 (41.0)**	75 (48.0)	
30–59 (stage 3)	NR	**261 (46.0)**	5435 (41.0)	<0.001	**40 (46.0)**	49 (32.0)	0.1202
15–29 (stage 4)	Excluded	**52 (9.0)**	690 (5.0)		**1 (1.0)**	2 (1.0)	
<15 (stage 5)	Excluded	**2 (0)**	86 (1.0)		**0 (0)**	0 (0)	
SBP, mm Hg							
Mean (SD)	122 (15)	**130 (21.3) n = 369**	136.9 (20.8) n = 7780	<0.001	**125 (18.8) n = 95**	132.6 (18.7) n = 145	0.0025
DBP, mm Hg							
Mean (SD)	NR	**77 (12.7) n = 369**	78.4 (11.4) n = 7780	0.0459	**76 (11.1) n = 95**	78.7 (10.2) n =145	0.0574

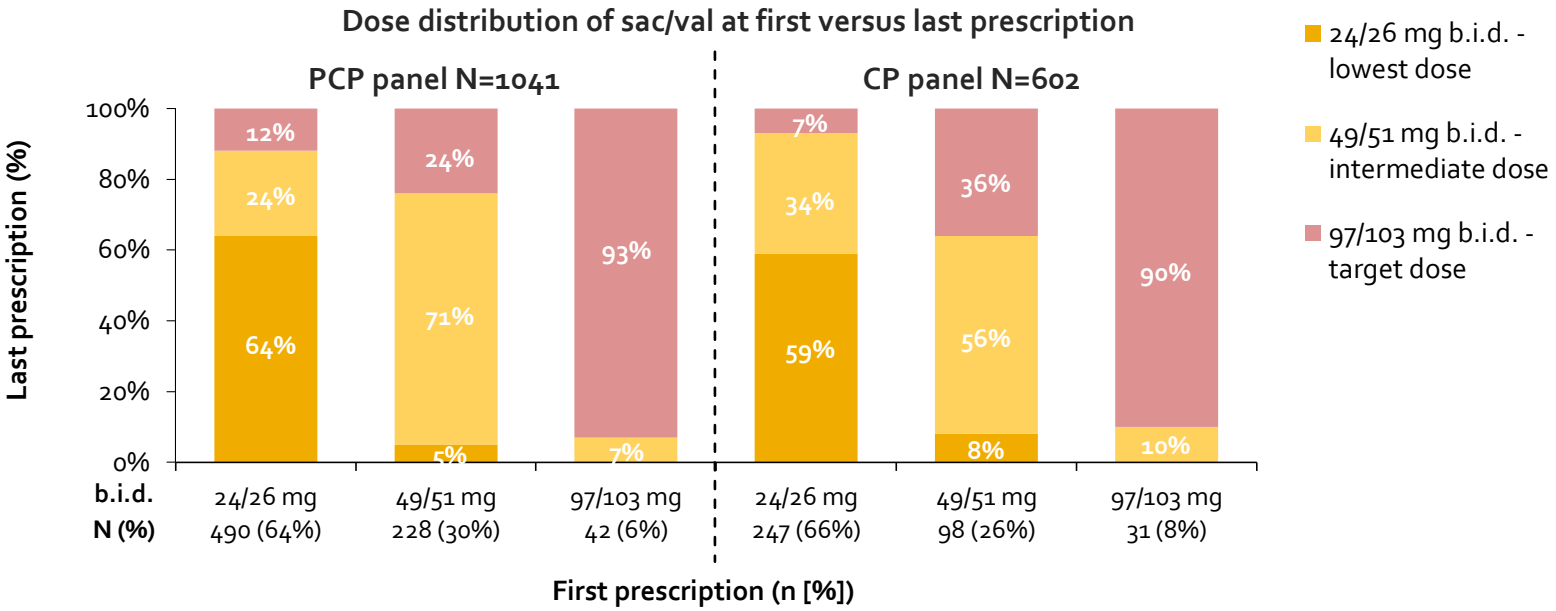
[a]In the PARADIGM-HF study, all characteristics presented were assessed in the run-in period before sac/val initiation[2]. p values are derived from the Student's t-test; *n (%) indicates the number of patients for whom data are available

CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NR, not reported; PARADIGM-HF, prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure; pHF-SoC, patients with prevalent heart failure receiving the standard of care (for patients with HFrEF NYHA class II–IV); sac/val, sacubitril/valsartan; SBP, systolic blood pressure; SD, standard deviation

1. Wachter R, et al Postgrad Med. 2018; DOI: 10.1080/00325481.2018.1442090
2. McMurray JJ, et al. N Engl J Med. 2014;371:993–1004

Inertia to up-titrate sac/val was observed, while most patients appeared to tolerate up-titration

- Up-titration of sac/val was observed in a minority of patients initiated on the lowest dose or the intermediate dose. Overall, ~20% of patients received the target dose (97/103 mg b.i.d.).
- Less than 10% of patients initiated on the intermediate or target dose were down-titrated, suggesting that the majority of patients are able to tolerate these doses.



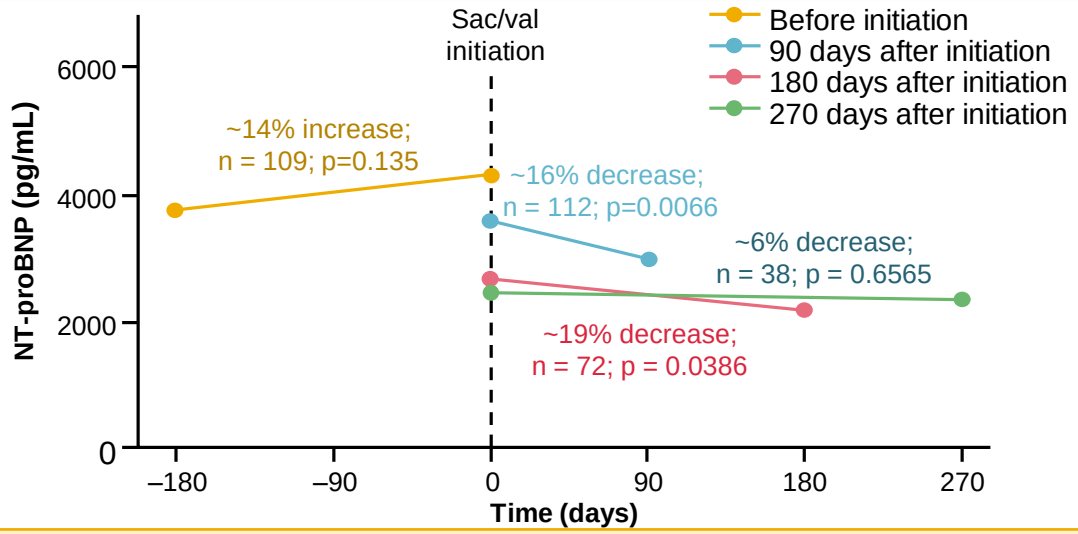
Only patients with minimum 2 prescriptions for sac/val were included in these analyses (n = 1136). p = 0.6345: patients who reached the target dose during follow-up; PCP panel vs CP panel.

b.i.d., twice daily; CP, cardiology practice; PCP, primary care practice; sac/val, sacubitril/valsartan

Wachter R, et al. Postgrad Med. 2018; DOI: 10.1080/00325481.2018.1442090

Sac/val treatment was associated with reductions in NT-proBNP levels

- Significant decreases in the NT-proBNP levels were observed at 90 and 180 days after sac/val initiation.



Clinical characteristic	No of patients n (No of observations)	Mean length of follow-up days[a]	Intercept at index (95% CI)	Mean change in value (95% CI)
NT-proBNP, pg/mL	119 (484)	131 (117)	−503[b]	−789, − 218[c]*

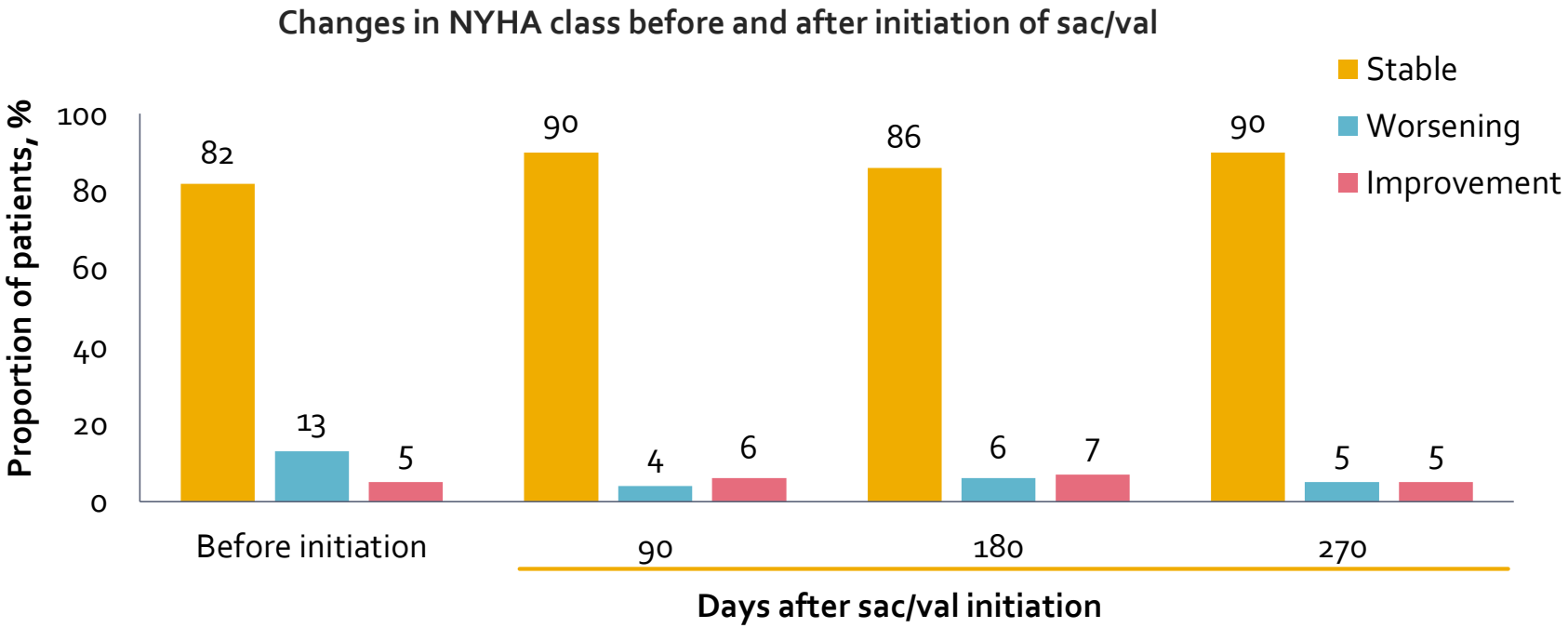
[a]Derived by subtracting the individual sac/val index date from the date of last observed patient record; [b]NT-proBNP values were log-transformed. The intercept at the index was back-transformed through exponentiation of the value. This value was then multiplied by the exponentiated value of sigma; [c]NT-proBNP values were log-transformed. The coefficient was back-transformed through exponentiation and represents a proportion that corresponds to a mean decrease of 3910 (3212, 4759) 95%, CI: 0.75 (0.82, 0.68); *Statistically significant (p<0.001).

CI, confidence interval; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PARADIGM-HF, prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure; sac/val, sacubitril/valsartan

Wachter R, et al. Postgrad Med. 2018; DOI: 10.1080/00325481.2018.1442090

The majority of patients had stable NYHA class over time, while sac/val reversed the increasing trend

- The trend towards increasing severity of symptoms observed during the 12-month pre-index period was reversed following sac/val initiation.



NYHA, New York Heart Association; PARADIGM-HF, prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure; SBP, systolic blood pressure; sac/val, sacubitril/valsartan

Wachter R, et al. Postgrad Med. 2018; DOI: 10.1080/00325481.2018.1442090

German RWE : Conclusion

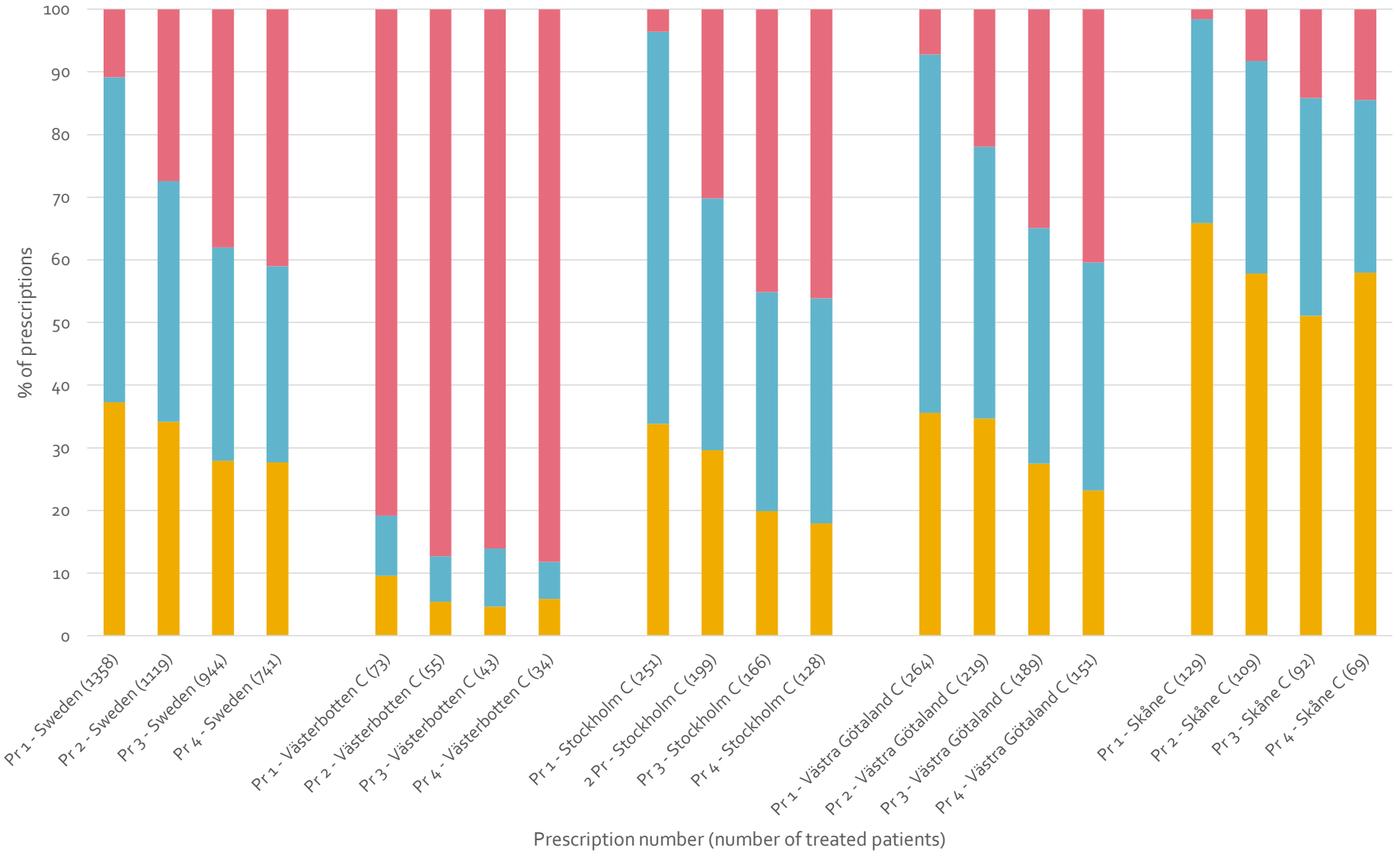
- Patients prescribed sac/val had similar baseline demographics and clinical characteristics to those from PARADIGM-HF
- Most patients were initiated on the lowest dose and stayed on lowest dose.
- Changes in clinical parameters before and after initiation mirrored findings from the PARADIGM-HF study.

Early real-world implementation of sacubitril/valsartan in Sweden

Ola Vedin, et al.

- Sacubitril/valsartan was reimbursed in Sweden since April 2016
- The Swedish Prescribed Drug Registry
- January 2016 and August 2017

Fig 1. Sacubitril/valsartan dose by number of dispensed prescriptions in Sweden and in the four counties with the highest number of treated patients



Sweden RWE: conclusion

- (1) Insufficient Sacubitril/valsartan dose uptitration
- (2) Highly variable Sacubitril/valsartan dosing between regions.

EUROPEAN SOCIETY OF CARDIOLOGY®

Heart Failure 2018 & World Congress on Acute Heart Failure

26 - 29 May 2018, Vienna - Austria

Sacubitril/valsartan initiation among renin-angiotensin aldosterone system inhibitor-naïve heart failure patients with reduced ejection fraction

April Mohanty, PhD

Research Health Scientist, Salt Lake City Veterans Affairs

Visiting Instructor, University of Utah

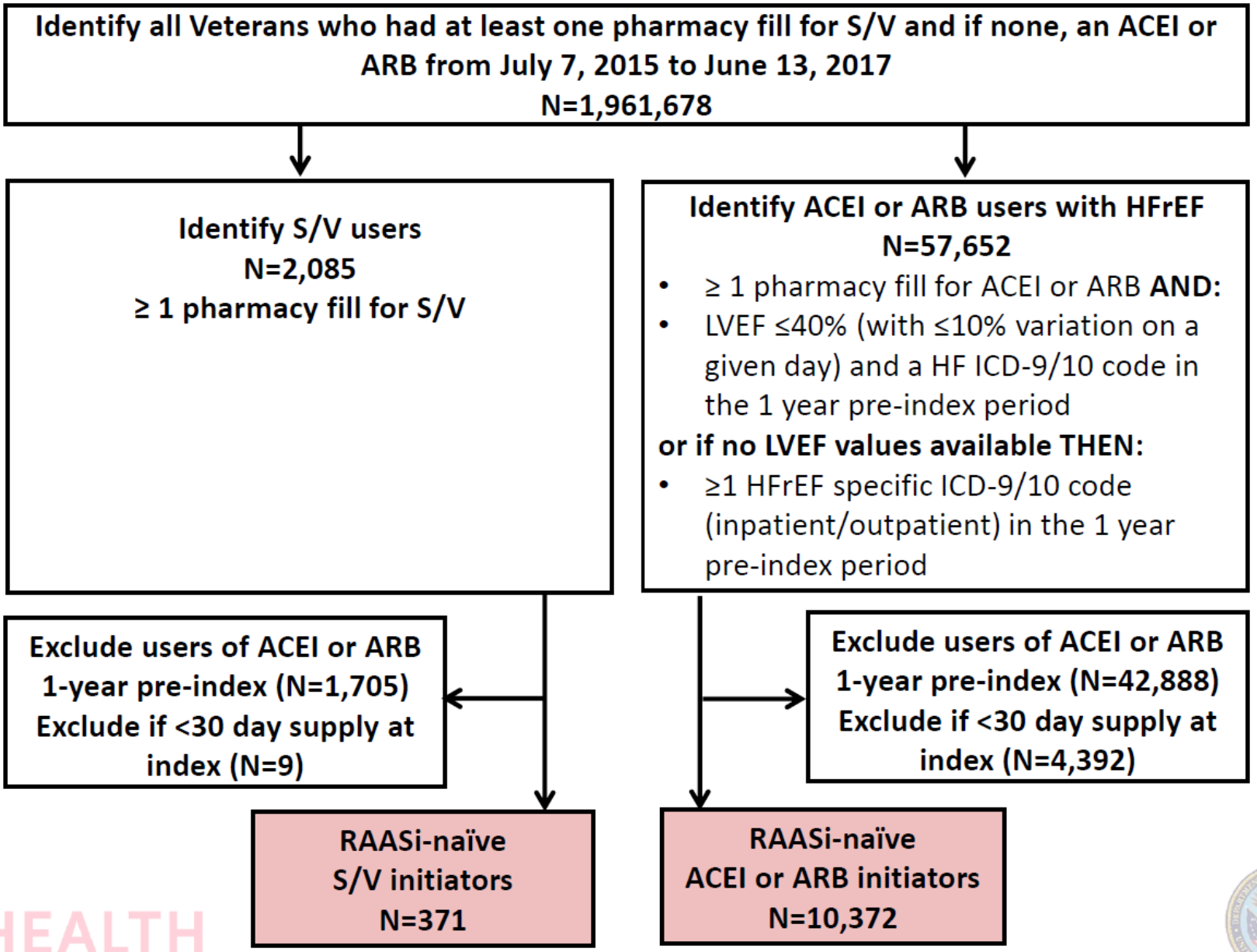
Salt Lake City, UT

May 26, 2018

European Society Cardiology-Heart Failure

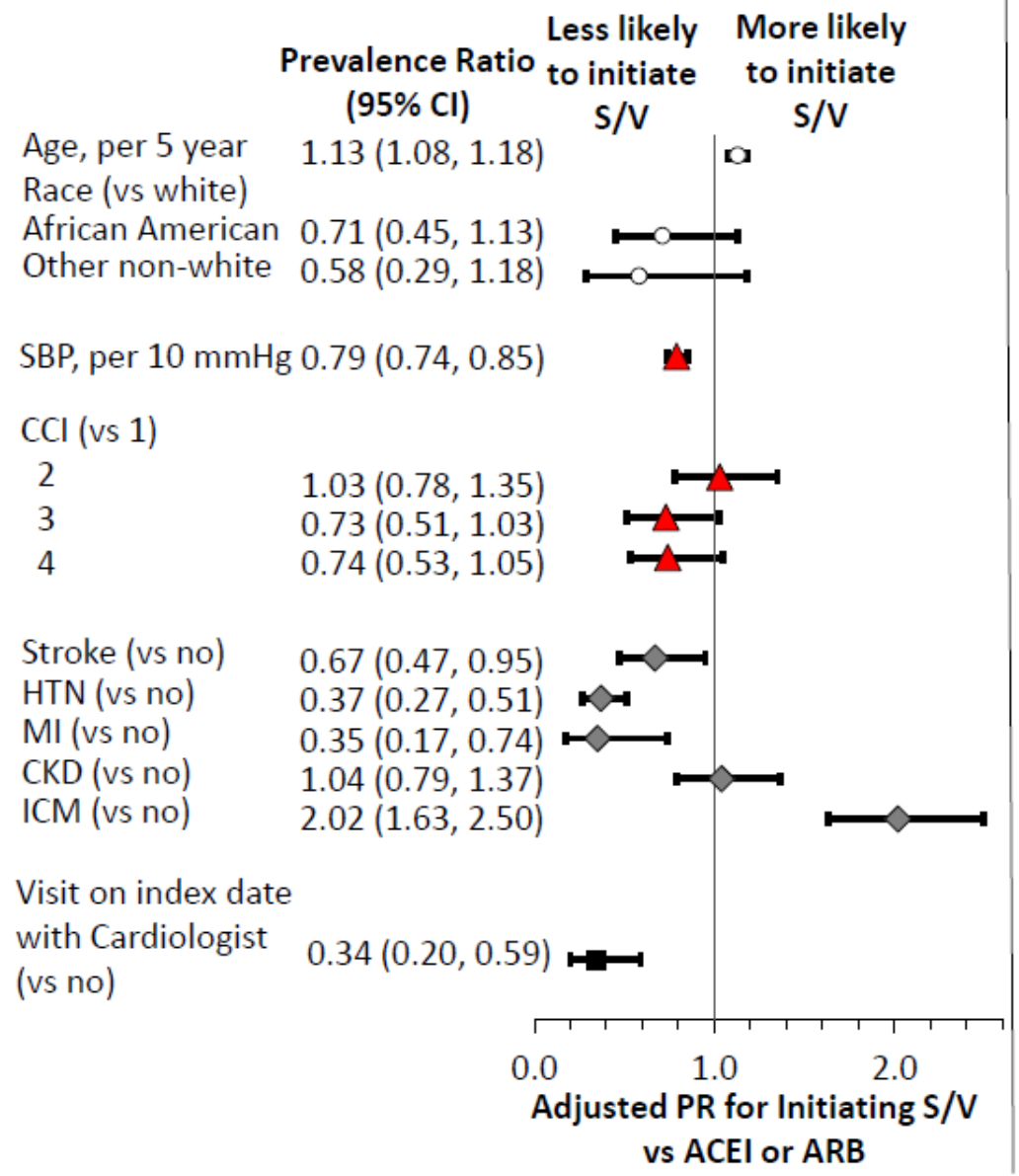
Rapid Fire Presentation

Study population identification

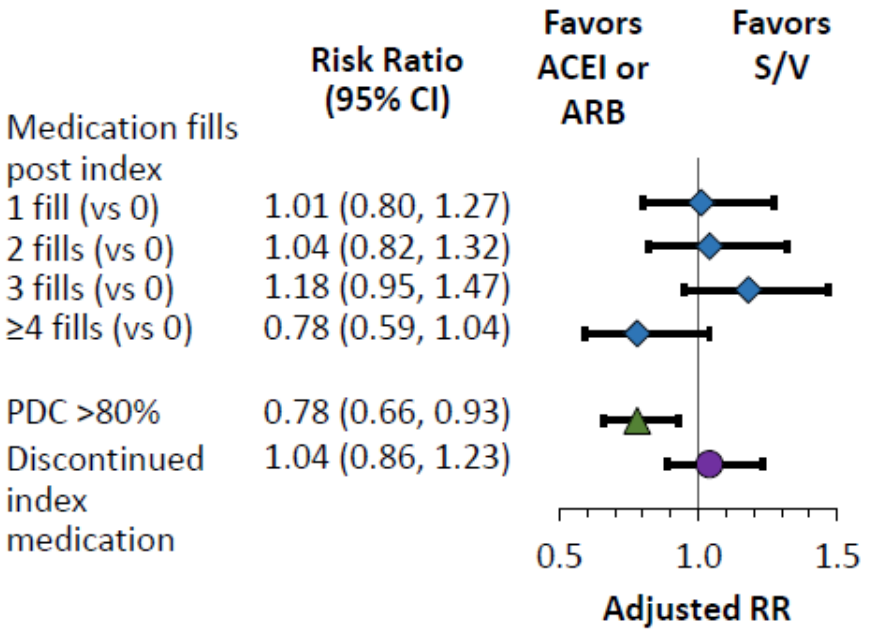


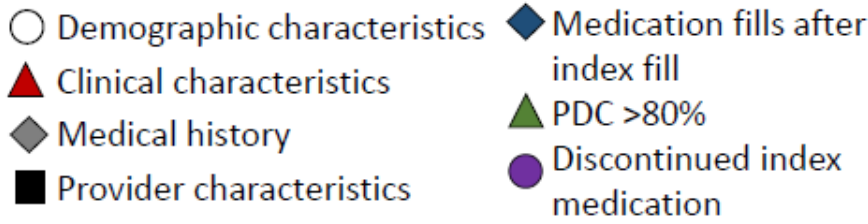
Results

Panel A. Baseline characteristics associated with initiating sacubitril/valsartan vs ACEI or ARB



Panel B. Adjusted risk ratios for 4-month follow-up medication adherence





Abbreviations: CCI, Charlson Comorbidity Index; CKD, Chronic Kidney Disease; HTN, Hypertension; ICM, Ischemic Cardiomyopathy; MI, Myocardial Infarction; PDC, Proportion of Days Covered; PR, Prevalence Ratio; RR, Relative Risk; SBP, Systolic Blood Pressure

USA RWE: Conclusion

- Among RAASi-naïve Veterans with HFrEF, 3.5% initiated S/V between July 2015 and June 2017
- Older Veterans and those with a history of ischemic cardiomyopathy were more likely to initiate S/V
- Veterans with a higher SBP, history of stroke, hypertension, and myocardial infarction, or who had a visit with a Cardiologist on the index date were less likely to initiate S/V
- Sac/Val adherence was similar to ACEI or ARB at four months post initiation
- These findings are important to the provider community as they suggest that there may be opportunities to optimize HFrEF pharmacotherapy for RAASi-naïve patients

Summary: from RCT to RWE

In PARADIGM-HF study proved Sacubitril/valsartan to be effective

Sacubitril/valsartan significantly reduced CV mortality or first HF hospitalization compared with enalapril (20%)

Sacubitril/valsartan to replace ACEI or ARB in persistent symptomatic HFrEF patients (AHA, ESC guideline)

Sacubitril/valsartan is first line therapy in AHA guideline

A gap between PARADIHM-HF and Real world practice.


Thank you for your attention