



ACC Latin America
Conference 2017



MEXICO CITY
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GLOBAL EXPERTS, LOCAL LEARNING



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Optimal pharmacological sequence of hormonal blockade in the treatment of HF.

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Governor Chile Chapter of ACC



DISCLOSURES INFORMATION



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I have not a financial relationship to disclosure



Trend in HF



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- Reduction in HF mortality (12%)
- Increase aging population
- Higher incidence of cardiac risk factors
- Higher prevalence of HF

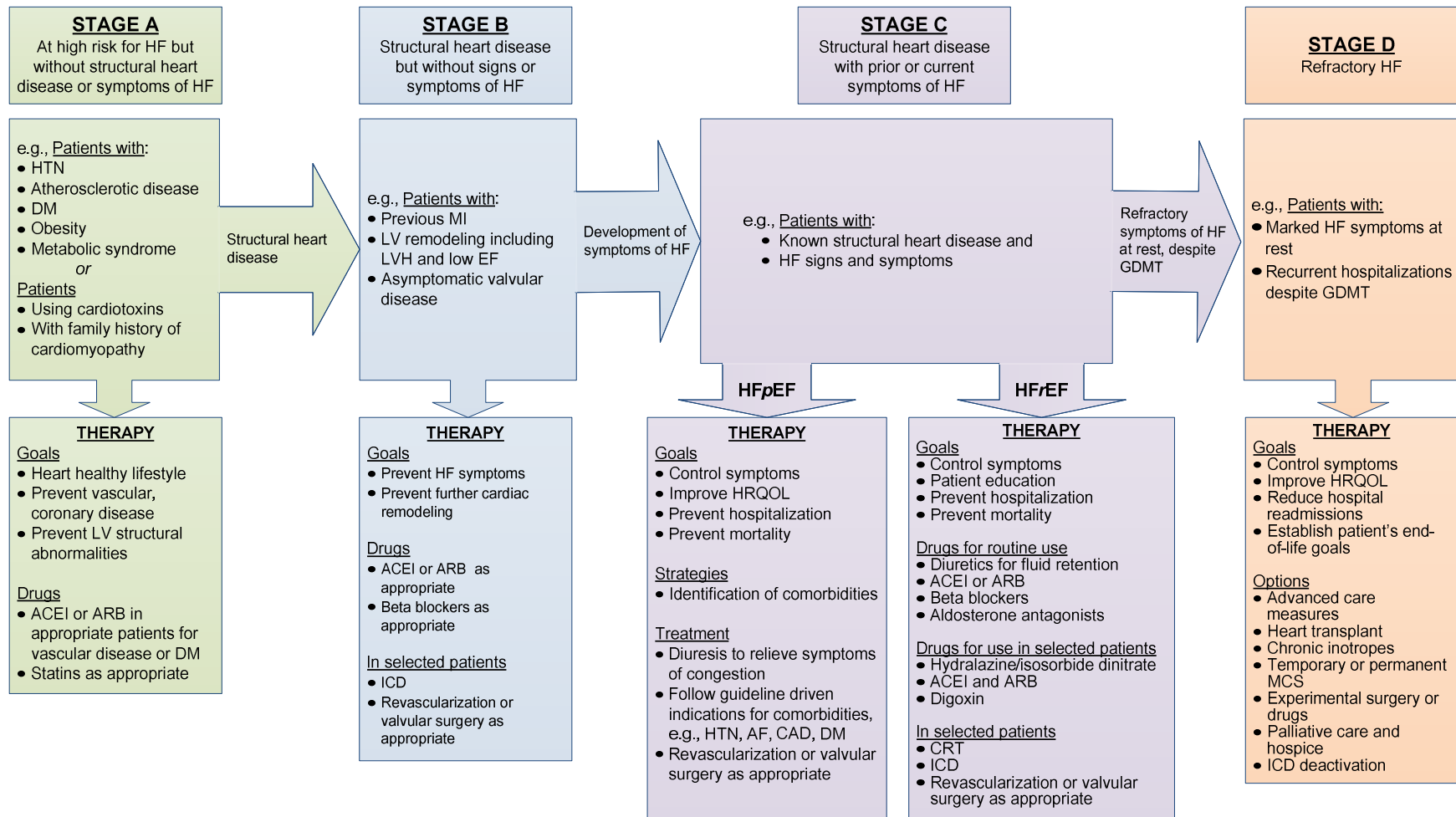
Source: Framingham, Olmsted County, Canada (ICES)





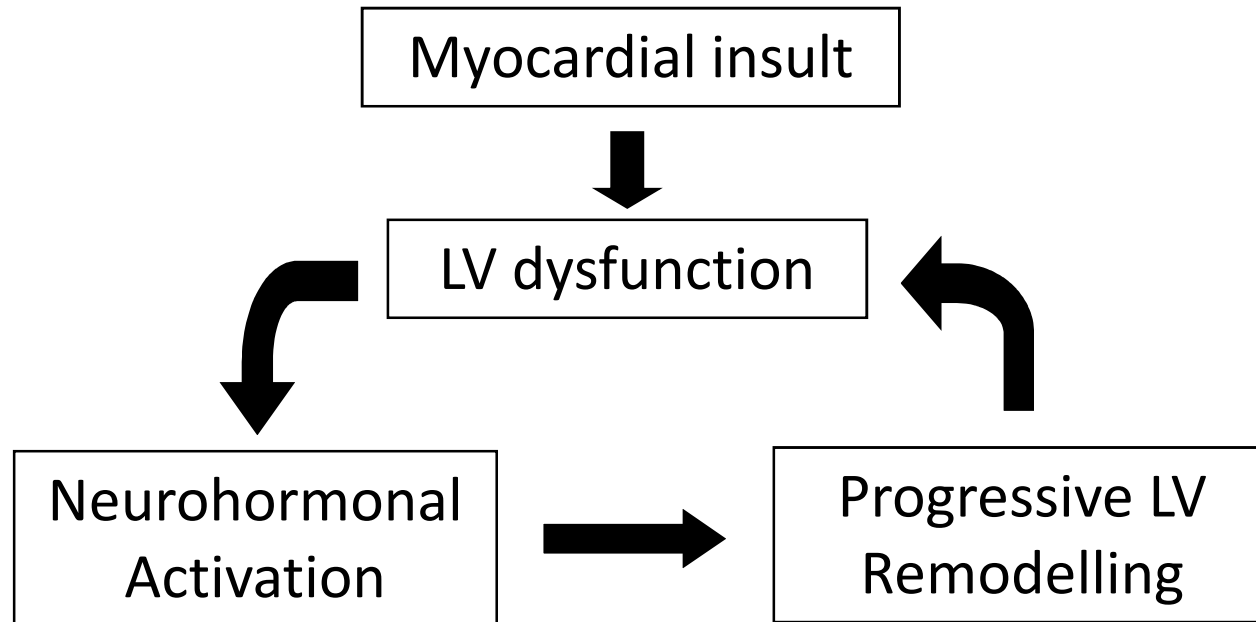
At Risk for Heart Failure

Heart Failure



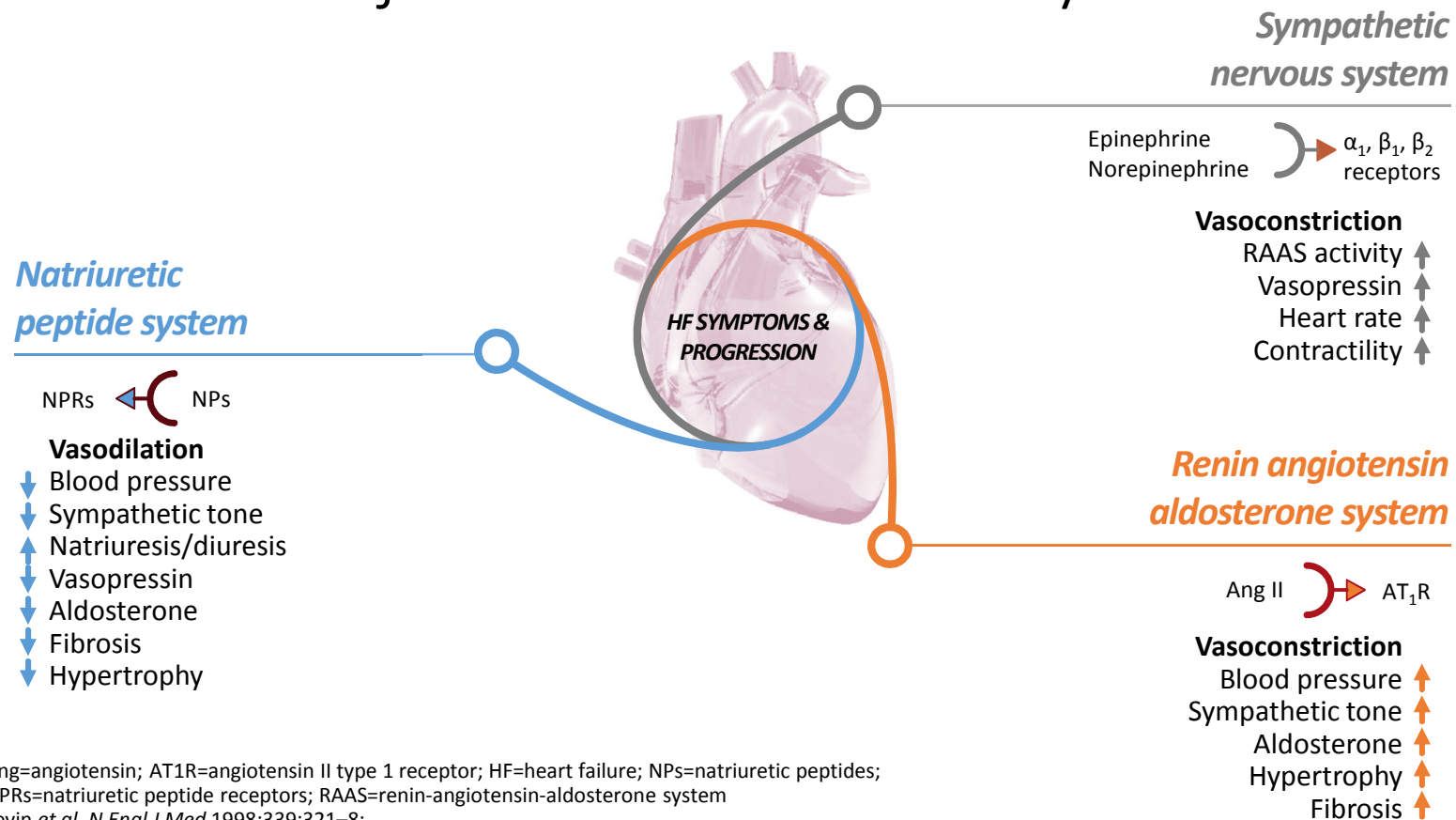
Neurohormonal
Activation and Rationale
For Standard Therapy for Systolic Heart
Failure

Neurohormonal activation is a central mechanism of progressive HF



- Initially supports the circulation
- Ultimately highly negative impact

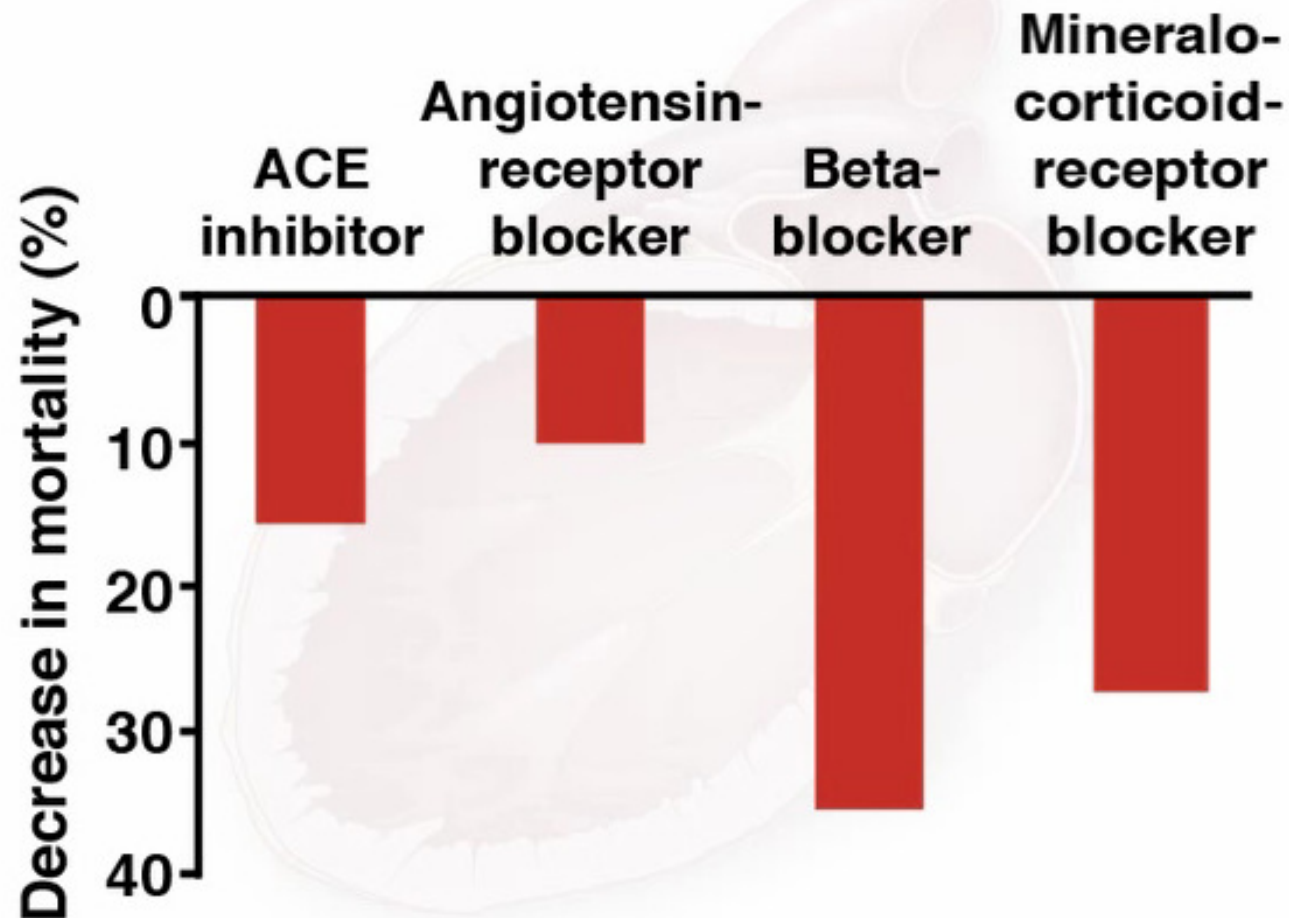
Decline In Systolic Function Leads To Activation Of Three Major Neurohormonal Systems



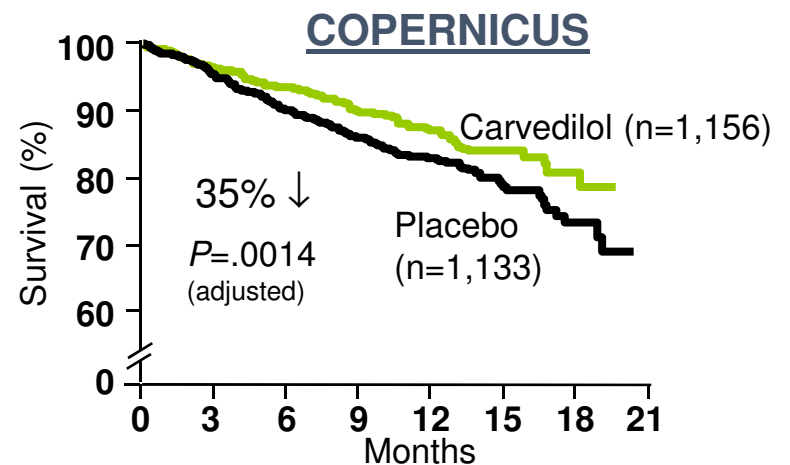
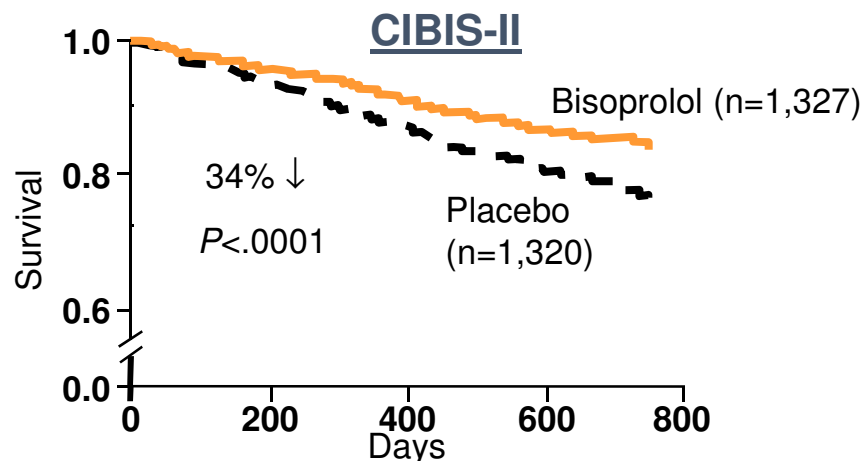
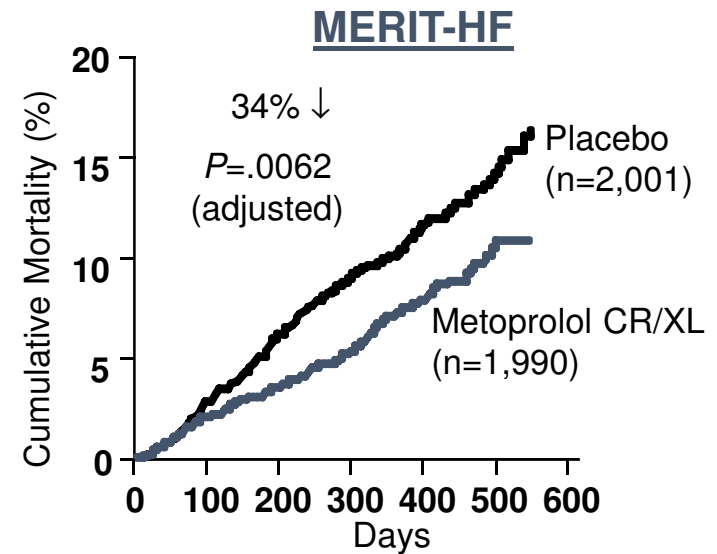
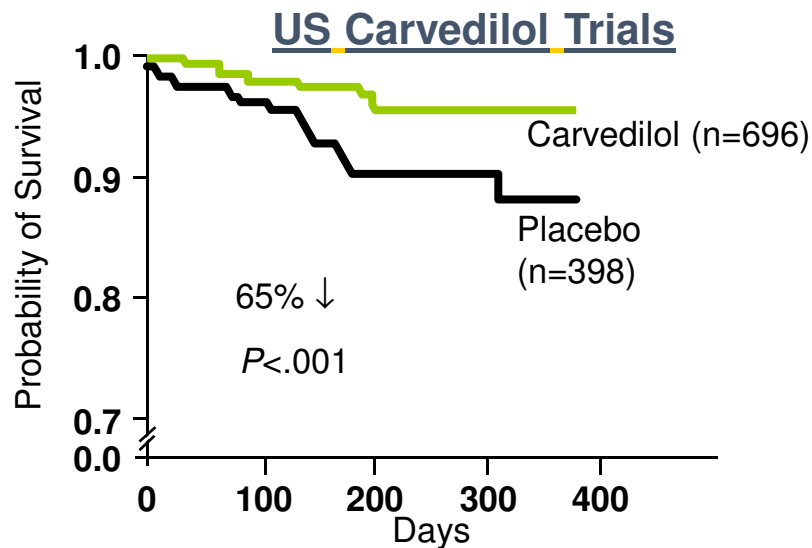
- Ang=angiotensin; AT_1R =angiotensin II type 1 receptor; HF=heart failure; NPs=natriuretic peptides; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system
- Levin *et al.* *N Engl J Med* 1998;339:321–8;
Nathisuwan & Talbert. *Pharmacotherapy* 2002;22:27–42;
Kemp & Conte. *Cardiovascular Pathology* 2012;365–371;
Schrier & Abraham. *N Engl J Med* 2009;341:577–85



Guideline-Directed Medical Therapy

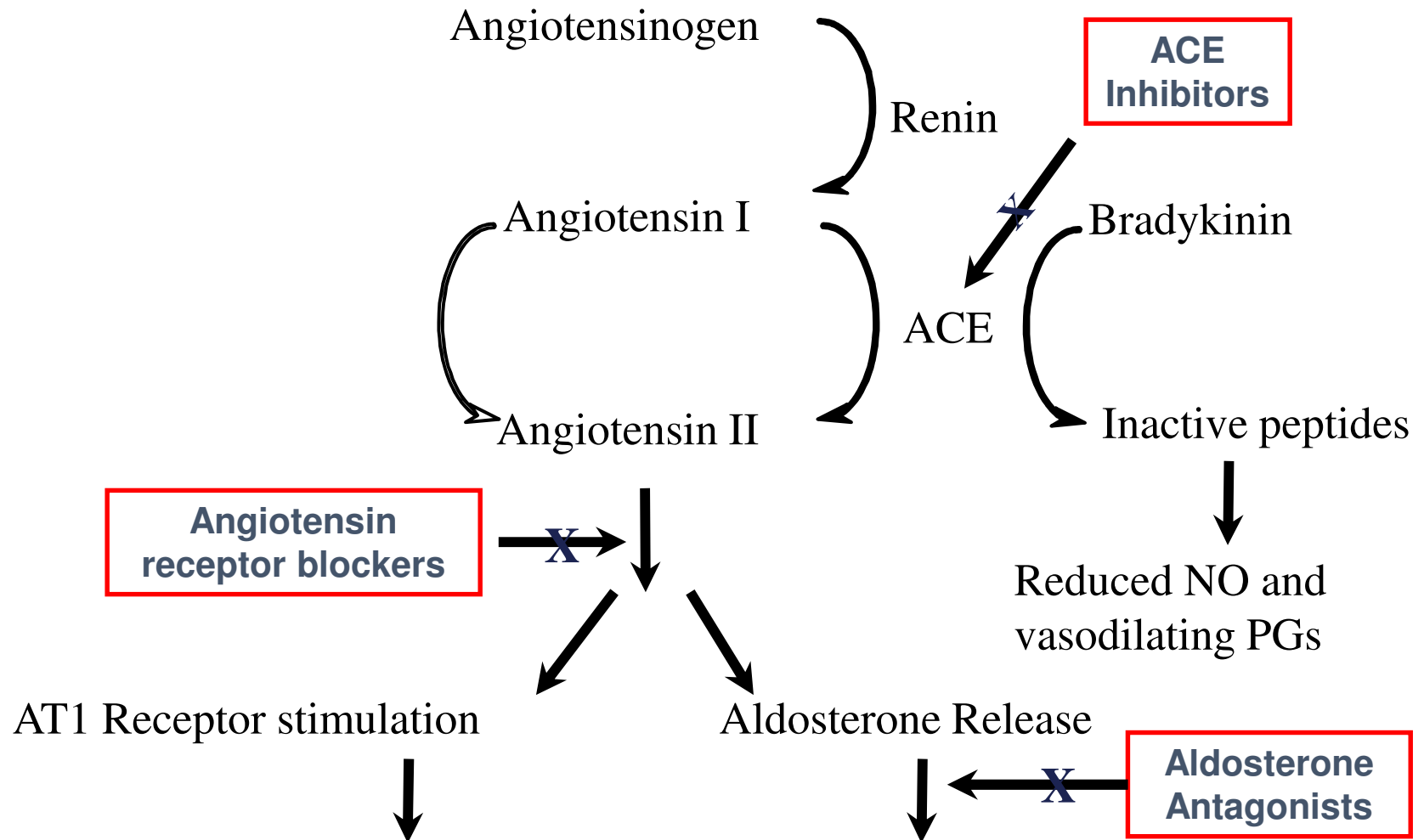


Addition of β -Blockade to ACE Inhibition Reduces Mortality in Heart Failure



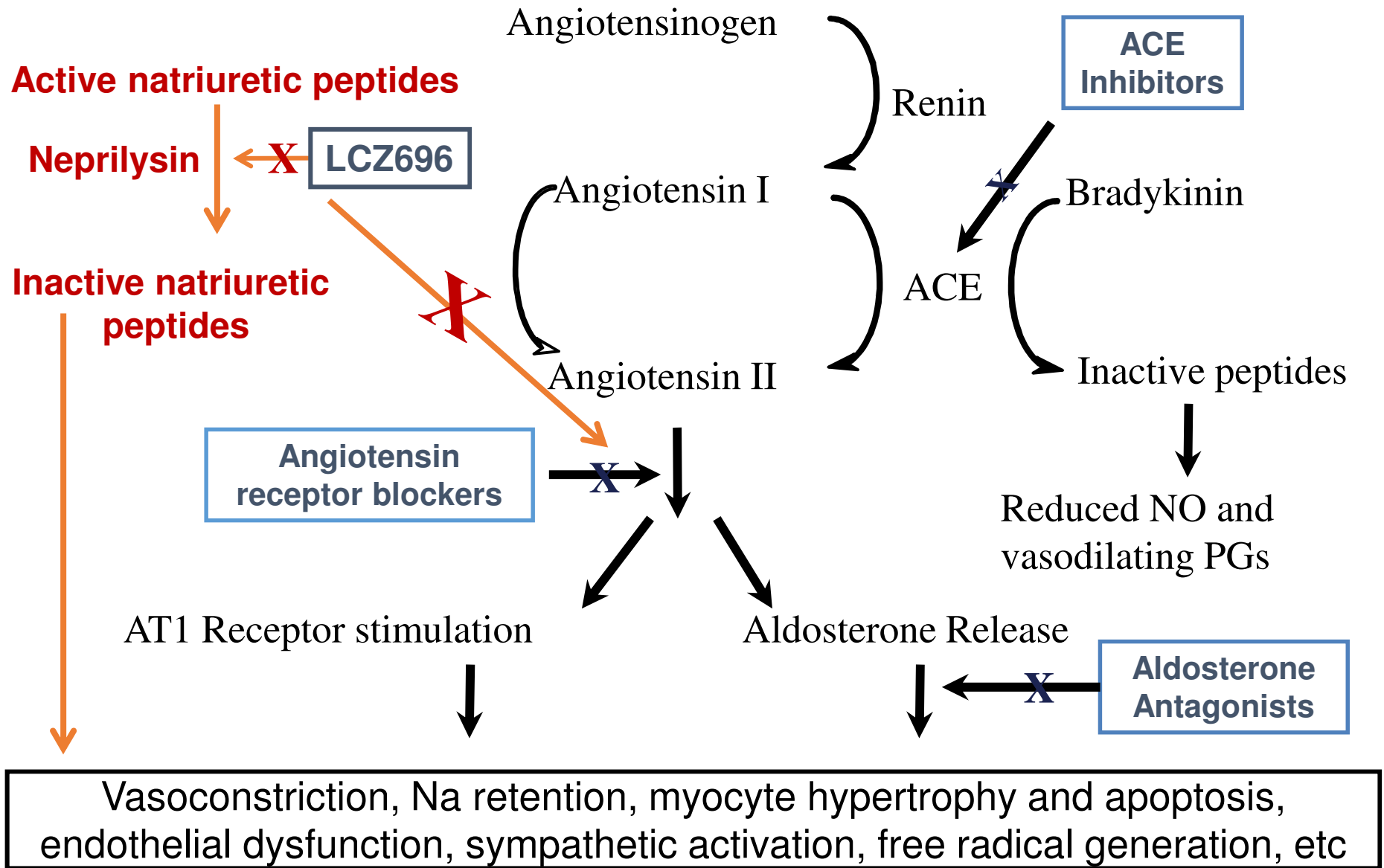
Packer M, et al. *N Engl J Med.* 1996;334:1349-1355. MERIT-HF Study Group. *Lancet.* 1999;253:2001-2007. CIBIS-II Investigators. *Lancet.* 1999;353:9-13. Packer M, et al. *N Engl J Med.* 2001;344:1651-1658.

Neurohormonal blockade in HF



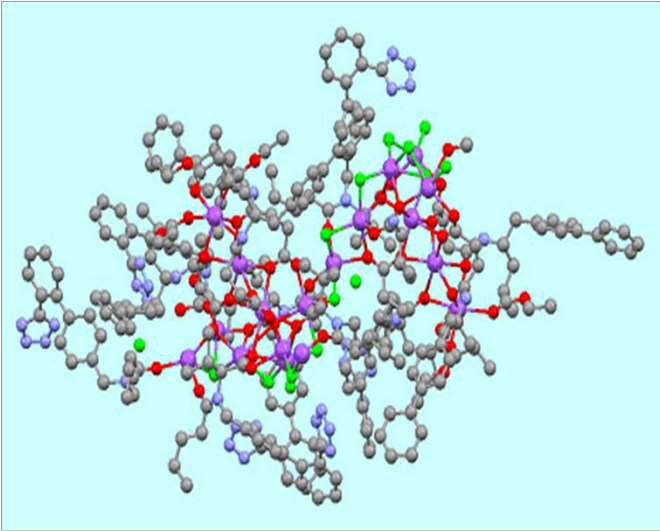
Vasoconstriction, Na retention, myocyte hypertrophy and apoptosis, endothelial dysfunction, sympathetic activation, free radical generation, etc

Neurohormonal blockade in HF – revisited again



LCZ696

- A novel ARNI compound -

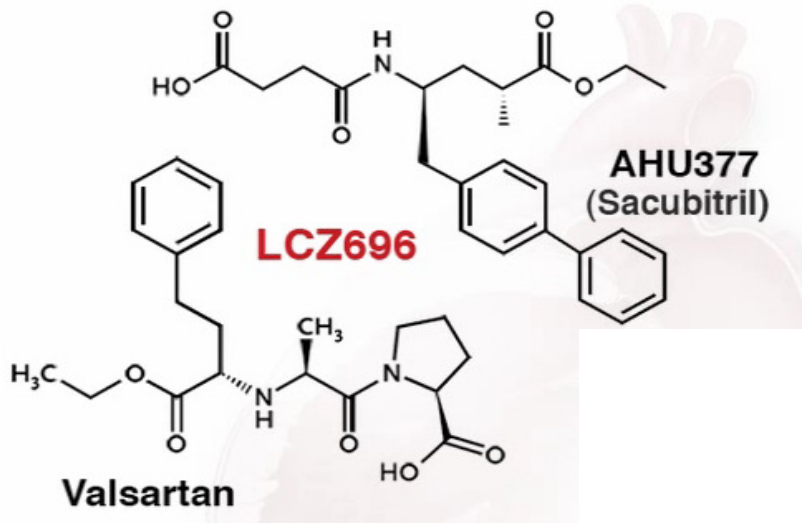


Complex with two active components:

- AHU377 pro-drug; further metabolized to the neprilysin inhibitor LBQ657

Plus

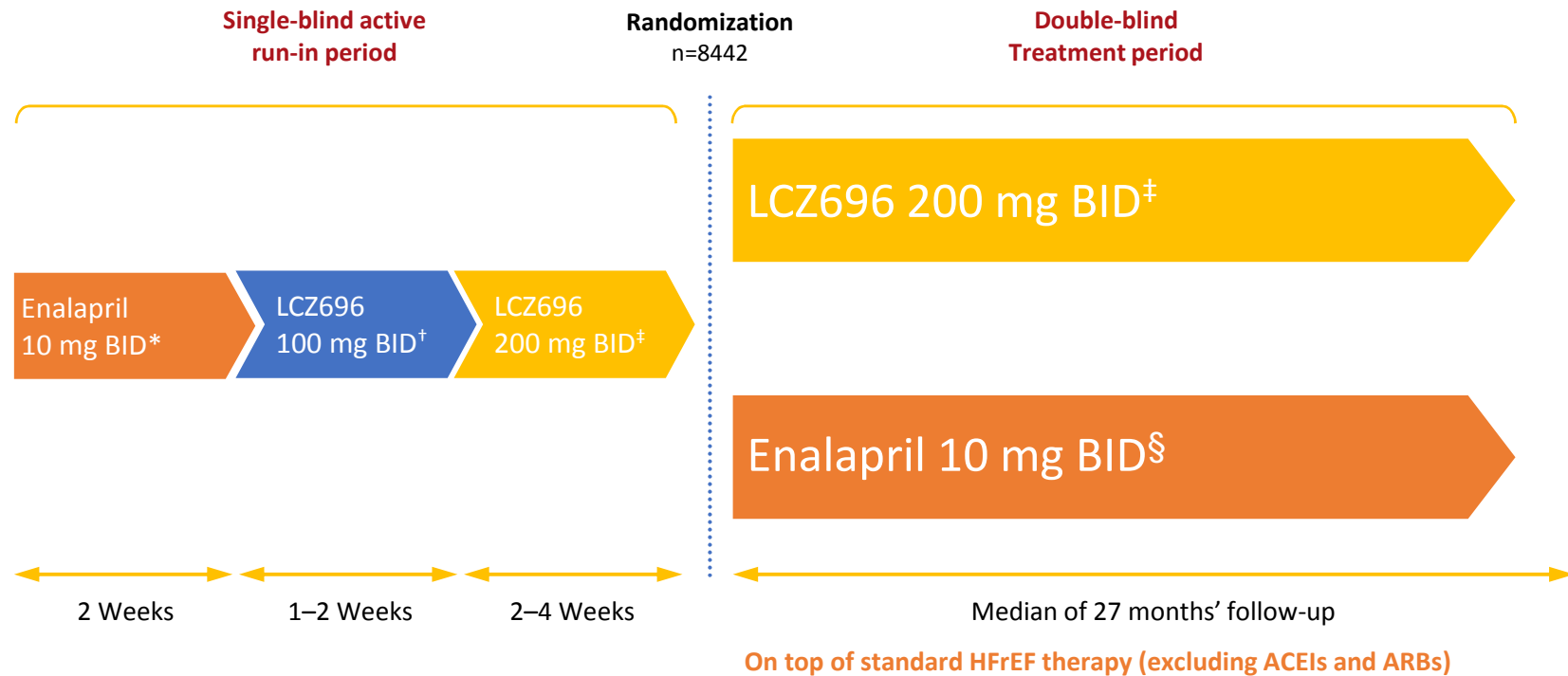
- Valsartan; angiotensin receptor (AT1) blocker



Now on to HF with reduced EF...

- The PARADIGM HF Study
 - Designed to assess whether the long-term effects of LCZ696 were superior to an ACEi in reducing morbidity and mortality
 - Powered to detect difference in mortality

PARADIGM-HF: Study Design



Note: Health Canada approved corresponding doses for LCZ696 are as follows:

LCZ696 100 mg: 48.6 mg sacubitril / 51.4 mg valsartan
 LCZ696 200 mg: 97.2 mg sacubitril / 102.8 mg valsartan

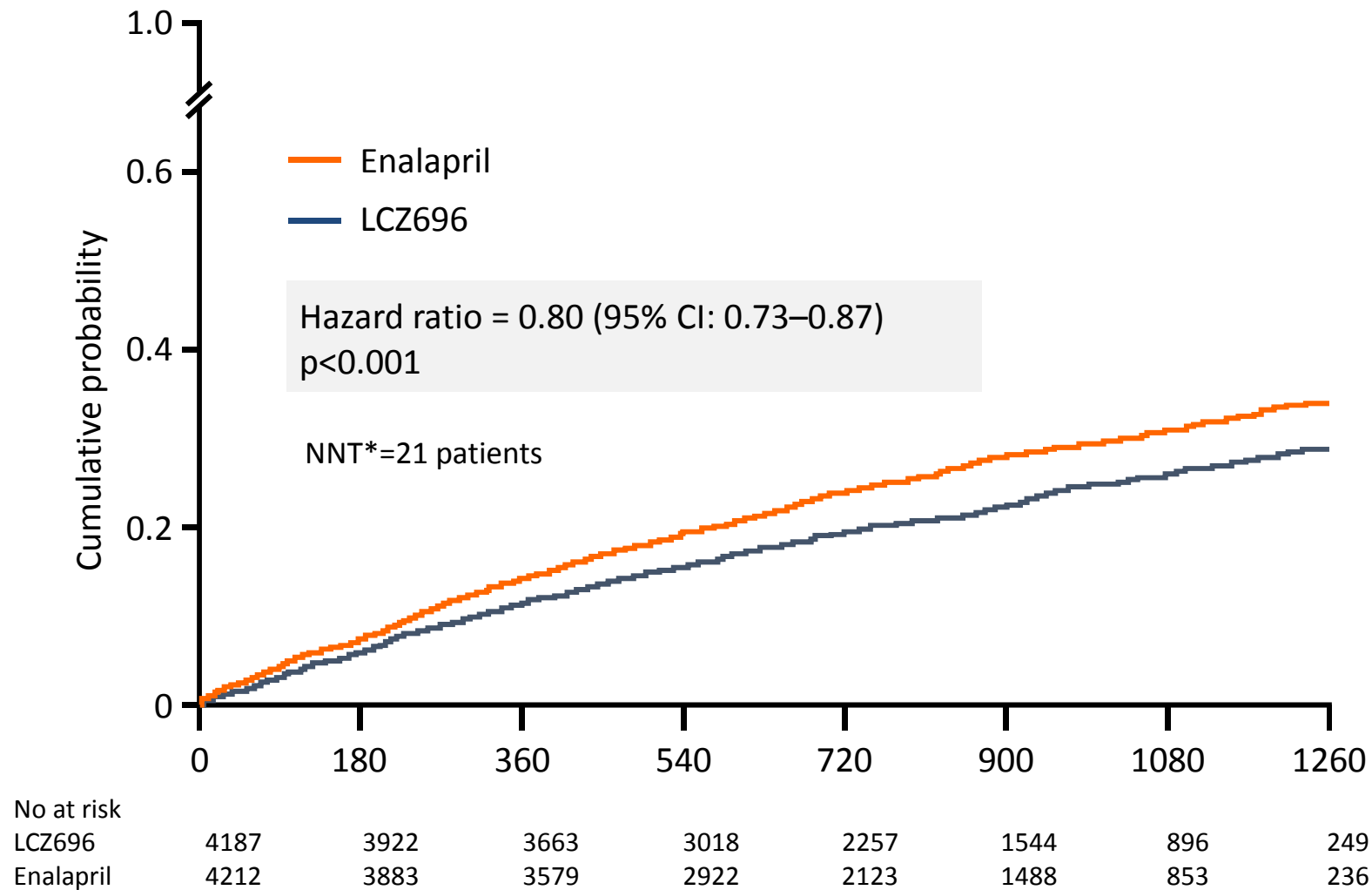
- *Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; [†]200 mg TDD; [‡]400 mg TDD; [§]20 mg TDD.
- McMurray *et al.* Eur J Heart Fail. 2013;15:1062–73; McMurray *et al.* Eur J Heart Fail. 2014;16:817–25; McMurray *et al.* N Engl J Med 2014;371 (11):993–1004.

Baseline Characteristics

Characteristic	LCZ696 (n=4187)	Enalapril (n=4212)
Age, years	63.8 ± 11.5	63.8 ± 11.3
Women, n (%)	879 (21.0)	953 (22.6)
Ischemic cardiomyopathy, n (%)	2506 (59.9)	2530 (60.1)
LV ejection fraction, %	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class, n (%)		
II	2998 (71.6)	2921 (69.3)
III	969 (23.1)	1049 (24.9)
SBP, mmHg	122 ± 15	121 ± 15
Heart rate, beats/min	72 ± 12	73 ± 12
NT pro-BNP, pg/mL (IQR)	1631 (885–3154)	1594 (886–3305)
BNP, pg/mL (IQR)	255 (155–474)	251 (153–465)
Treatments at randomization, n (%)		
Diuretics	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
β-blockers	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonists	2271 (54.2)	2400 (57.0)
ICD	623 (14.9)	620 (14.7)
CRT	292 (7.0)	282 (6.7)

Primary endpoint:

Death from CV causes or first hospitalization for HF



Safety

Event, n (%)	LCZ696 (n=4187)	Enalapril (n=4212)	p-value
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with SBP <90 mmHg	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/L	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/L	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema (adjudicated by a blinded expert committee)			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalized without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	---

Fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an AE

Sacubitril/Valsartan prevents disease progression

- Subanalysis of PARADIGM HF
 - Sacubitril/Valsartan reduced ED visits, hospitalization, inotrope use
 - Less intensification of HF therapy
 - Lower troponin and NT pro BNP levels
 - Improved symptom scores

Too good to be true?

- Single trial
- Target doses may not be achievable in real world
- Low baseline use of ICD and CRT
 - May mitigate benefit with increase device use
- Higher incidence of hypotension vs. ACEi
- Not representative of patients with more advanced HF
- Enalapril dose?

Concerns

COST: ISSUE IN LATIN AMERICA



Yancy, CW, et al.
Heart Failure Focused Update on Pharmacological Therapy

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An 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

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI		
COR	LOE	Recommendations
I	ACE: A	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (<i>Level of Evidence: A</i>) (9-14), <u>OR</u> ARBs (<i>Level of Evidence: A</i>) (15-18), <u>OR</u> ARNI (<i>Level of Evidence: B-R</i>) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
	ARB: A	
	ARNI: B-R	
III: Harm	B-R	ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).
III: Harm	C-EO	ARNI should not be administered to patients with a history of angioedema.

