NEW CONCEPTS IN MEDICAL MANAGEMENT OF CHRONIC HEART FAILURE

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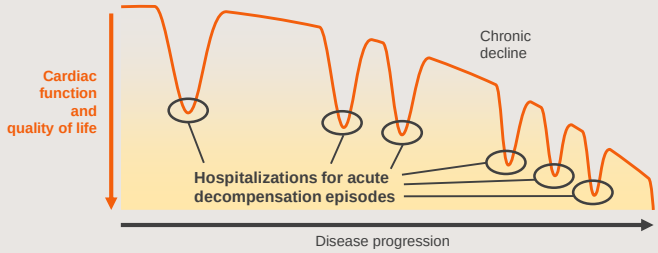
HF is a complex syndrome involving multiple organ systems and is associated with high re-hospitalization and mortality rates

- HF is a chronic progressive condition, punctuated by acute episodes
- Each acute event results in further organ damage; myocardial and renal damage occurring during such episodes may contribute to progressive left ventricular and/or renal dysfunction
- Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality



1. Mihai Gheorghiade, Leonardo De Luca, Gregg C. Fonarow, et al. Pathophysiologic targets in the early phase of acute heart failure syndromes. Am J Cardiol 2005;96:11–17;

2. Gheorghiade & Pang. Acute heart failure syndromes .J Am Coll Cardiol 2009;53:557–73

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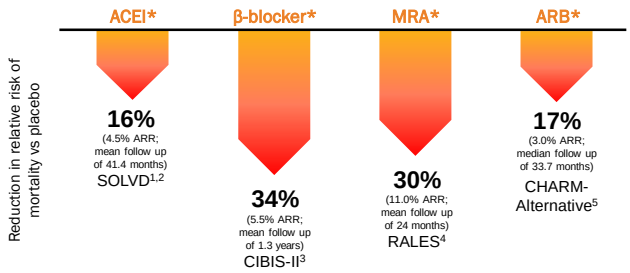
Mortality in HFrEF remains high despite the introduction of new therapies that improve survival

- 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[6–8]

*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) enroled chronic HF patients with LVEF≤40%

ACEI=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; HF=heart failure; 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. Granger et al. Lancet 2003;362:772–6; 4. CIBIS-II Investigators. Lancet 1999;353:9–13; 5. Pitt et al. N Engl J Med 1999;341:709-17;–50; 6. Go et al. Circulation 2014;129:e28-e292; 7. Yancy et al. Circulation 2013;128:e240–327; 8. Levy et al. N Engl J Med 2002;347:1397–402

Heart failure Mortality statistics

Mortality rates in heart failure are high even for patients compliant with the best available treatments[1]

~50% DIE WITHIN 5 YEARS OF DIAGNOSIS[2]

When heart failure symptoms are stabilised by current treatments, it may seem that patients are doing well, but the neurohormonal imbalance underlying heart failure is still silently occurring, resulting in disease progression.[1]

The impact of heart failure on individuals is significant, and the worldwide prevalence is high

1. Fauci AS, Braunwald E, Kasper DL, et al, eds. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2008. 2. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. JAMA. 2004;292(3):344-350.

Goals of Treatment as per ESC-HF guidelines

- Improve the clinical status of patients with HF
- Improve functional capacity and quality of life
- Prevent hospital admission and reduce mortality

ESC-HF, European Society of Cardiology-Heart Failure

Ponikowsk,Adriaan,StefanD.Ankeri et al. Eur Heart J. 21 May 2016. doi:10.1093/eurheartj/ehw128

2016 ESC Guideline: The Principal 8 Changes from the 2012 Guidelines

1. New term for patients with HF and a left ventricular ejection fraction (LVEF) that ranges from 40 to 49% — *'HF with midrange EF* (HFmrEF)'; we believe that identifying HFmrEF as a separate group will stimulate research into the underlying characteristics, pathophysiology and treatment of this population;
2. Clear recommendations on the diagnostic criteria for HF with reduced EF (HFrEF), HFmrEF and HF with preserved EF (HFpEF);
3. A new algorithm for the diagnosis of HF in the non-acute setting based on the evaluation of *HF probability*;
4. Recommendations aimed at prevention or delay of the development of overt HF or the prevention of death before the onset of symptoms;
5. Indications for the use of the new compound **sacubitril/valsartan**, the first in the class of angiotensin receptor neprilysin inhibitors (ARNIs);
6. Modified indications for cardiac resynchronization therapy (CRT);
7. The concept of an early initiation of appropriate therapy going along with relevant investigations in acute HF that follows the 'time to therapy' approach already well established in acute coronary syndrome (ACS);
8. A new algorithm for a combined diagnosis and treatment approach of acute HF based on the presence/absence of congestion/hypoperfusion.

ACC, American College of Cardiology; AHA, American Heart Association; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker, ARNI, angiotensin receptor neprilysin inhibitor; CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; HFSA, Heart Failure Society of America; HFrEF, HF with reduced ejection fraction; NYHA, New York Heart Association

Ponikowsk,Adriaan,StefanD.Ankeri et al. Eur Heart J. 21 May 2016. doi:10.1093/eurheartj/ehw128

2016 ESC HF guidelines: **Disease-modifying** therapies in HFrEF

Drug class	Drugs
ACEi	Captopril, enalapril, lisinopril, ramipril, trandolapril
Beta-blockers	Bisoprolol, carvedilol, metoprolol succinate (CR/XL)
ARBs	Candesartan, valsartan, losartan
MRAs	Eplerenone, spironolactone
ARNI	**Sacubitril/valsartan**

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Ponikowsk,Adriaan,StefanD.Ankeri et al. Eur Heart J. 21 May 2016. doi:10.1093/eurheartj/ehw128

2016 ESC Guideline – Sacubitril / Valsartan

- ESC-HF guidelines provide **strong Class I** recommendation for sacubitril/valsartan

Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) HFrEF		
Recommendations	Class	Level
An ACEi is recommended, in addition to a beta blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
A beta blocker is recommended, in addition an ACEi, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death	I	A
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACEi and a beta-blocker, to reduce the risk of HF hospitalization and death	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEi to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEi, a beta-blocker and an MRA*	I	B

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

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Ponikowsk,Adriaan,StefanD.Ankeri et al. Eur Heart J. 21 May 2016. doi:10.1093/eurheartj/ehw128

Sacubitril/valsartan in management of ventricular arrhythmias

Recommendations for the management of ventricular tachyarrhythmias in heart failure		
Recommendations	Class	Level
Treatment with beta-blocker, MRA and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias (as for other patients) (Section 10.2).	I	A

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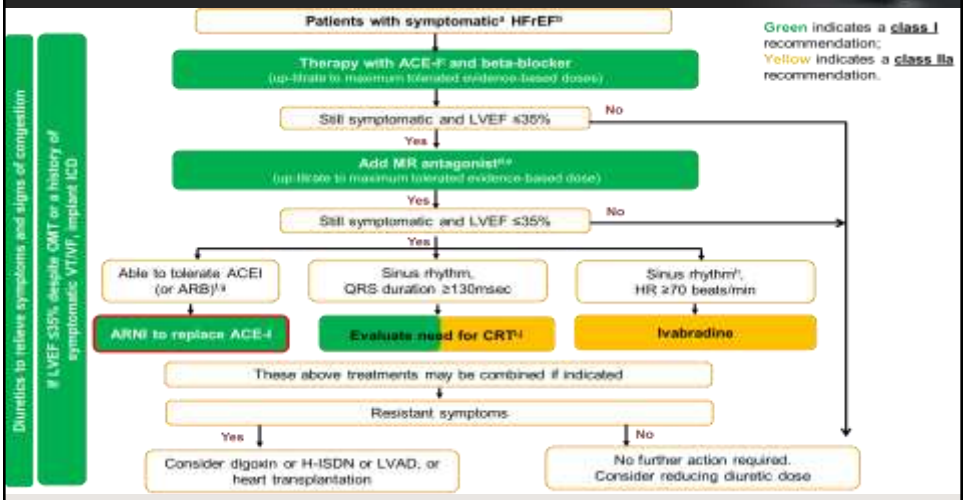
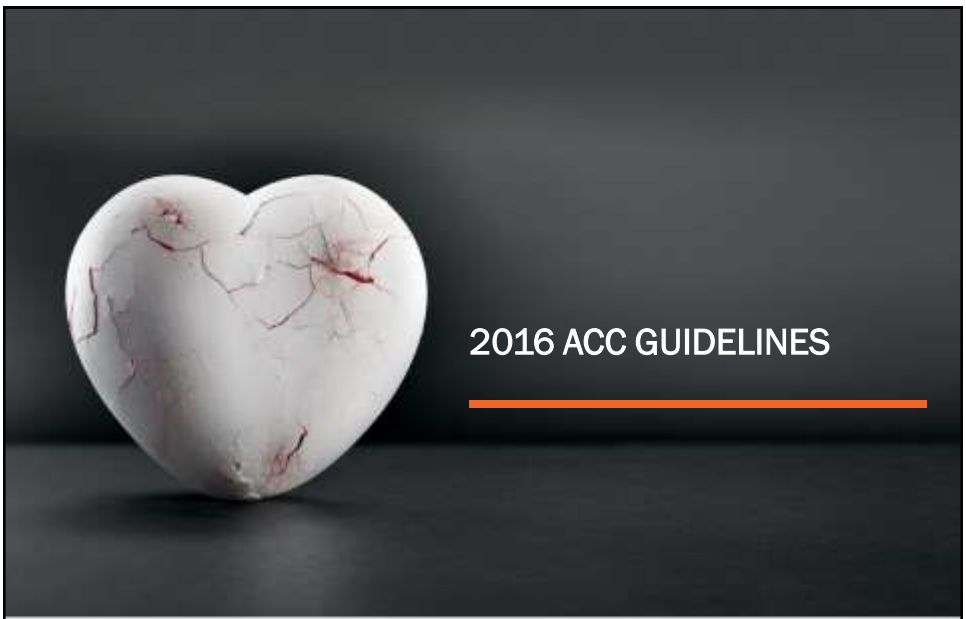
2016 ESC Guideline

Treatment Algorithm



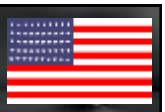
[a]Symptomatic=NYHA Class II-IV; [b]HFrEF=LVEF<40%; [c]If ACEI not tolerated/contra-indicated, use ARB; **[d]If MR antagonist not tolerated/contra-indicated, use ARB; [e]With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP >250 pg/ml or NTproBNP >500 pg/ml in men and 750 pg/ml in women); [f]With an elevated plasma NP 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 (individualized decision)

Ponikowsk,Adriaan,StefanD.Ankeri et al. Eur Heart J. 21 May 2016. doi:10.1093/eurheartj/ehw128



ACC/AHA/HFSA Focused Update

Sacubitril/valsartan level of evidence



- ACC/AHA/HFSA guidelines provide **strong Class I** recommendation for sacubitril/valsartan

Pharmacological treatments for Stage C* HFrEF

Recommendations	Class	Level
The clinical strategy of inhibition of the renin-angiotensin system with ACEi (Level of Evidence: A), OR ARBs (Level of Evidence: A), OR ARNI (Level of Evidence: B-R) in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality.	I	ACEi: A ARB: A ARNI: B-R
The use of ACEi is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality	I	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 ACEi because of cough or angioedema	I	A
In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality	I	B-R

*Stage C: structural heart disease with prior or current symptoms of HF

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Clyde W. Yancy , Mariell Jessup, Biykem Bozkurt et al. J Am Coll Cardiol. Published 21 May 2016. doi:10.1016/j.jacc.2016.05.011

Summary of NICE recommendations

- **Recommendation:** Sacubitril/valsartan recommended as an option for treating symptomatic HFrEF in patients
  - •With NYHA II−IV
  - •LVEF<35%
  - •Already on a stable dose of ACEi or ARBs
- Treatment should be started by a **HF specialist** with access to multidisciplinary HF team
- Dose titration to be performed by most appropriate HF team member
- PARADIGM-HF showed sacubitril/valsartan to be more clinically effective than enalapril at reducing hospitalizations and improving overall and CV mortality in HFrEF patients
- Manageable adverse event profile in HF patients
- Sacubitril/valsartan considered to represent a cost effective use of UK NHS resources

NICE technology appraisal adoption support for sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction – insights from the NHS Health technology adoption programme.Published: 15 July 2016.nice.org.uk

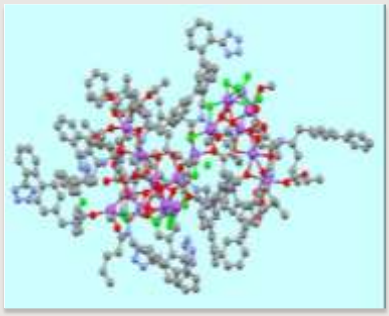
LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI)

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

- ARNI=angiotensin receptor neprilysin inhibitor; AT_1=angiotensin II type 1

- 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:[2,3]
  - sacubitril (AHU377) – a pro-drug; further metabolized to the neprilysin inhibitor LBQ657, and
  - valsartan – an AT_1 receptor blocker

  in a 1:1 molar ratio



3D LCZ696 structure[2]

1. Michael J Bloch, Jan N Basile Combination angiotensin receptor blocker-neutral endopeptidase inhibitor provides additive blood pressure reduction over angiotensin receptor blocker alone.J Clin Hypertens 2010;12:809–812
2. Jessie Gu, PhD, Adele Noe, PhD, Priya Chandra, PhD, et al Pharmacokinetics and Pharmacodynamics of LCZ696, a Novel Dual-Acting Angiotensin Receptor–Neprilysin Inhibitor (ARNi).J Clin Pharmacol 2010;50:401–414
3. Langenickel & Dole. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. Drug Discov Today: Ther Strateg 2012:9 e131–9

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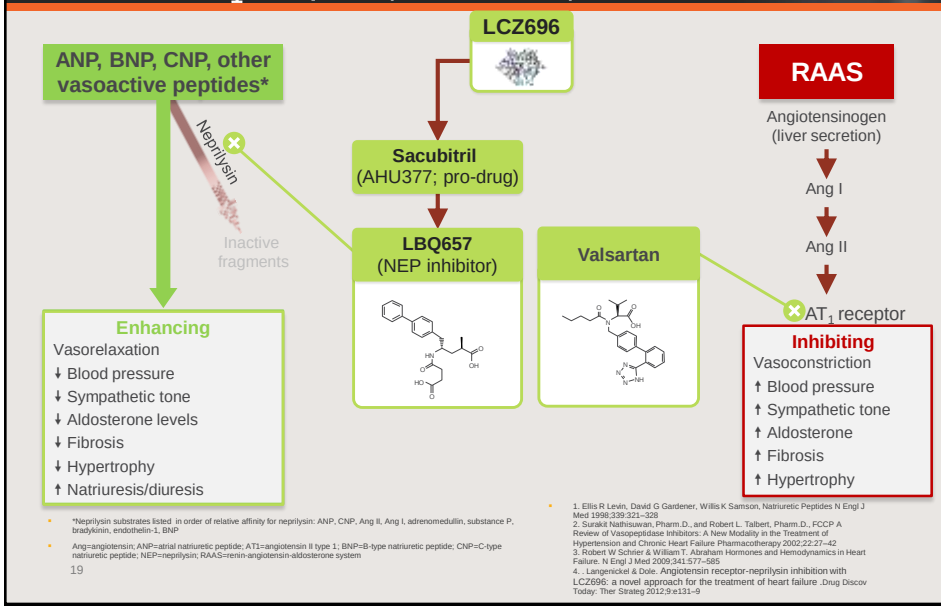
LCZ696 simultaneously inhibits neprilysin (via LBQ657) and blocks AT_1 receptors (via valsartan)[1-4]



- *Neprilysin substrates listed in order of relative affinity for neprilysin: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP
- Ang=angiotensin; ANP=atrial natriuretic peptide; AT1=angiotensin II type 1; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide; NEP=neprilysin; RAAS=renin-angiotensin-aldosterone system

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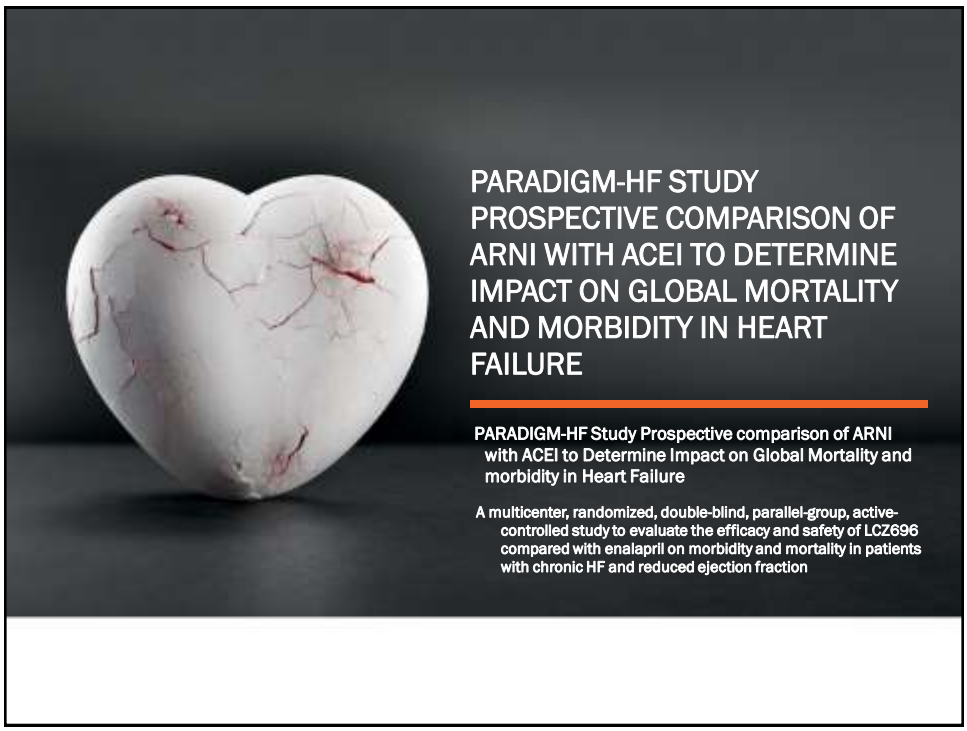
- 1. Ellis R Levin, David G Gardener, Willis K Samson, Natriuretic Peptides N Engl J Med 1998;339:321–328
2. Surakit Nathisuwan, Pharm.D., and Robert L. Talbert, Pharm.D., FCCP A Review of Vasopeptidase Inhibitors: A New Modality in the Treatment of Hypertension and Chronic Heart Failure Pharmacotherapy 2002;22:27–42
3. Robert W Schrier & William T. Abraham Hormones and Hemodynamics in Heart Failure. N Engl J Med 2009;341:577–585
4. . Langenickel & Dole. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure .Drug Discov Today: Ther Strateg 2012;9:e131–9



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

PARADIGM-HF:

- Is the first study to test the effect of LCZ696 on morbidity and mortality in patients with HFrEF
  - primarily evaluates whether simultaneous angiotensin receptor neprilysin inhibition with **LCZ696** compared with **enalapril**, in addition to conventional HF treatment…

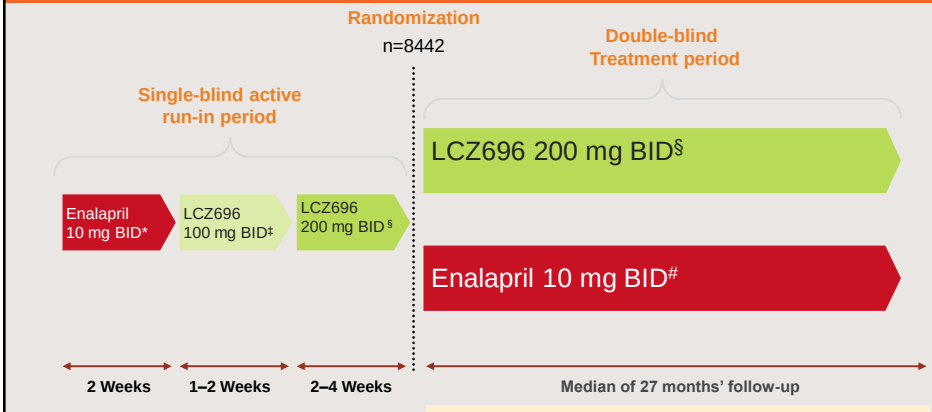
    …delays **time to first occurrence of either CV death or HF hospitalization**…

    …in patients with stable NYHA FC II–IV HF and *reduced* ejection fraction (**LVEF ≤40%***)
- Determined the place of the ARNI LCZ696 as an alternative to an ACEI (enalapril) in patients with chronic systolic HFrEF
- May change the approach to neurohormonal modulation in HFrEF

- *The ejection fraction entry criteria was lowered to ≤35% in a protocol amendment. ACEI=angiotensin-converting enzyme inhibitor; ARNI=angiotensin receptor neprilysin inhibitor; CV=cardiovascular; FC=functional class; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; NYHA= New York Heart Association

- McMurray,packer,Desai et al. Dual angiotension receptor neprylisin inhibition as ana alternative to angiotension converting enzyme inhibition in
- patients with chronic systolic heart failure rationale for design of the prospective comparison of ARNI and ACEI to determine impact on global mortality and morbidity in heart failure trial(PARADIGM).Eur J Heart Fail 2013;15:1062–73

PARADIGM-HF: study design[1-3]



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. ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; 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

patients with chronic systolic heart failure rationale for design of the prospective comparison of ARNI ans ACEI to determine impact on global mortality and morbidity in heart failure trial(PARADIGM).Eur J Heart Fail 2013;15:106273

2.McMurray .Packer.Desai.et al. Baseline characteristics and treatment of patients in Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF

Eur J Heart Fail 2014;16:817–25

3.McMurray,packer,Desai.et al. Angiotension neprylsin inhibition versus enalpril in heart failure.N Engl J Med 2014;371:993–1004

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]

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]

1. McMurray JJ, Packer M, Desai AS et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF).Eur J Heart Fail 2013;15:1062–72.Shannon M. Dunlay, Nilay D. Shah, Qian Shi et al. Lifetime Costs of Medical Care After HeartFailure Diagnosis. Circ Cardiovasc Qual Outcomes 2011;4:68–75.3. McMurray, Jan Ostergren, Karl Swedberg et al. Effects of Candesartan in patients with chronic heart failure and reduced left ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767–77.4. Karl Swedberg, Michel Komajda, Michael Böhm et al. Ivabradine and outcomes in chronic heart failure (SHIFT):a randomised placebo-controlled study Lancet 2010;376:875–88.5. Faiez Zannad, John J.V. McMurray, Henry Krum et al. Eplerenone in Patients with Systolic Heart Failureand Mild Symptoms N Engl J Med 2011;364:11–2.6. Martin R Cowie ,Stefan D Anker,John GF Cleland et al. Improving care for patients with acute heart failure Before, during and after hospitalization.Oxford Health policy Forum 2014;7. Sharon Ann Hunt, William T. Abraham, Marshall H. Chin et al. 2009Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Reportof the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation J Am Coll Cardiol 2009;53:e1–90. 8. Clyde W. Yancy, Mariell Jessup, Biykem Bozkurt et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure : A Reportof the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.Circulation 2013;128:e240–327. 9. Fernando Rodriguez-Artalejo, José R. Banegas,Pilar Guallar-Castillón. Epidemiology of Heart Failure Rev Esp Cardiol 2004;57:163–70

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 I_f Inhibitor Ivabradine Trial

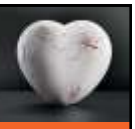
PARADIGM-HF: Secondary Objectives

- To assess whether LCZ696 was superior to enalapril in:
  - improving quality of life (assessed by KCCQ score)
  - delaying time to all-cause mortality
  - delaying time to new-onset atrial fibrillation
  - delaying time to decline of renal function as defined by:
    - 50% decline in eGFR from baseline, or
    - >30 mL/min/1.73 m^2 decline in eGFR relative to baseline and to a value of <60 mL/min/1.73 m^2 (indicating the development of moderate renal dysfunction), or
    - development of end-stage renal disease

McMurray JJ, Packer M, Desai AS et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF).Eur J Heart Fail 2013;15:1062–73

eGFR=estimated glomerular filtration rate; KCCQ=Kansas City Cardiomyopathy Questionnaire; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

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; 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

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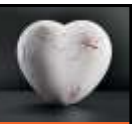
PARADIGM-HF: Key Exclusion Criteria

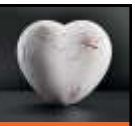


- History of angioedema
- eGFR <30 mL/min/1.73 m2 at screening, end of enalapril run-in or randomization,
  or a >35% decrease in eGFR between screening and end of enalapril run-in or between screening and randomization
- Serum potassium >5.2 mmol/L at screening OR >5.4 mmol/L at the end of the enalapril run-in or end of the LCZ696 run-in
- Requirement for treatment with both ACEI and ARBs
- Symptomatic hypotension, SBP <100 mmHg at screening, OR SBP <95 mmHg at end of enalapril run-in or at randomization
- Current acute decompensated HF
- History of severe pulmonary disease
- Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid, or other major CV surgery, PCI, or carotid angioplasty within the 3 months prior to screening

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; PCI=percutaneous coronary intervention; SBP=systolic blood pressure

McMurray JJ, Packer M, Desai AS et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF).Eur J Heart Fail 2013;15:1062–73

Summary of Results – Efficacy



- **Primary outcome**
  - 20% reduction in CV death or HF hospitalization with LCZ696 compared with enalapril
    - 20% reduction in CV mortality
    - 21% reduction in HF hospitalization
- **Secondary outcomes**
  - 16% reduction in all-cause mortality with LCZ696 vs enalapril
  - LCZ696 superior to enalapril in reducing symptoms and physical limitations of HF (indicated by KCCQ score)
  - No significant difference in incidence of new onset atrial fibrillation between treatment groups
  - No significant difference in protocol-defined decline in renal function between treatment groups

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Conclusions from the PARADIGM-HF results publication

- "…angiotensin receptor–neprilysin inhibition with sacubitril/valsartan was superior to ACE inhibition alone in reducing the risks of death and of hospitalization for HF"
- "The magnitude of the beneficial effect of sacubitril/valsartan, as compared with enalapril, on CV mortality was at least as large as that of long-term treatment with enalapril, as compared with placebo."
- "This robust finding provides strong evidence that combined inhibition of the angiotensin receptor and neprilysin is superior to inhibition of the RAAS alone in patients with chronic HF."
- "…results are applicable to a broad spectrum of patients with HF, including those who are currently taking an ACE inhibitor or ARB or who are likely to be able to take such an agent without having unacceptable side effects."

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CV, cardiovascular; HF, heart failure; PARADIGM-HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; RAS, renin-angiotensin system

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


THANK YOU