The Changing Landscape of HF Management

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Objectives

Review guidelines for pharmacological HF therapy

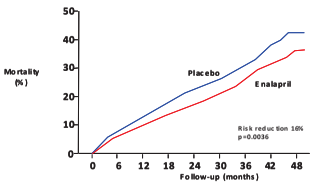
Review recent advancements in HF therapy

Discuss the practical approaches to implementing the guidelines

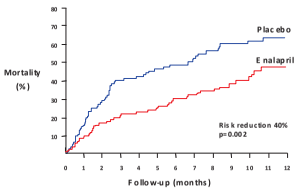
ACE - Inhibitors

All patients with EF < 40% should be treated with and ACEI

CCS - Guidelines: Class I, Level A

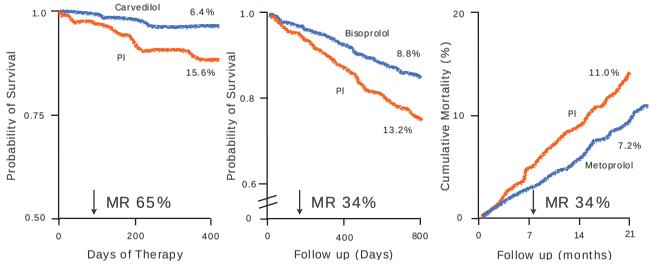


SOLVD Treatment
NEJM 1991; 325:293-302



CONSENSUS-I
NEJM 1987; 316:1429-35

Beta-Blockers in HF

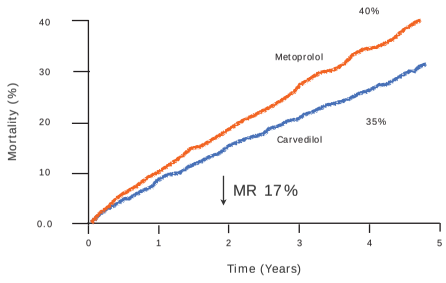


US Carvedilol HF Study
NEJM - 1996, 334: 1349-55

CIBIS-II
Lancet - 1999, 353: 9-13

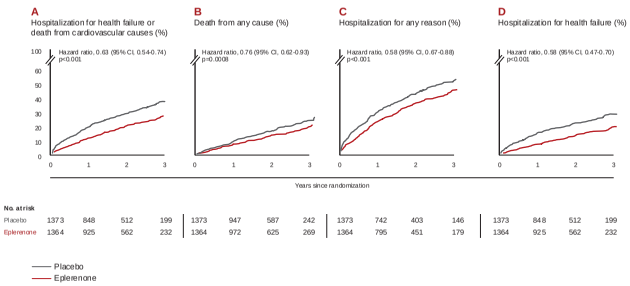
MERIT-HF
Lancet - 1999, 353: 2001-7

COMET Trial



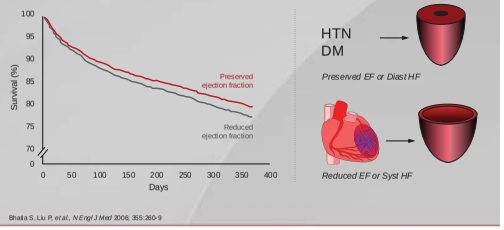
Poole-Wilson et al - Lancet 2003

Mineralocorticoid Receptor Blockade: EMPHASIS-HF



Zannad et al - New Engl J Med 2011

HFpEF & HFrEF
Different Diseases With The Same Prognosis?



HFpEF = Compatible Presentation + Preserved EF + ↑ ***Filling Pressures***

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

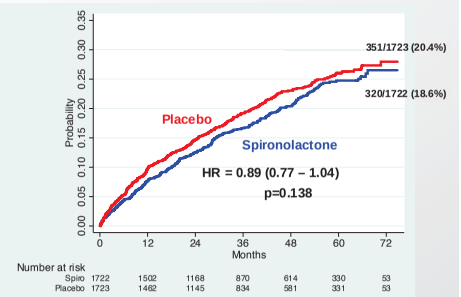
TOPCAT Funded by the NHLBI

- **Objective**
  - To determine if treatment with spironolactone can produce a clinically meaningful reduction in the composite endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure, compared with placebo, in adults with HF-Preserved EF.
- **Inclusions:**
  Symptomatic Heart Failure, Age ≥ 50, LVEF ≥ 45%, stratified according to:
  - Hospitalization within the past year for management of heart failure, or
  - Elevated natriuretic peptides (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)
- **Major Exclusions:**
  eGFR<30 mL/min/1.7m^2, serum potassium ≥5 mmol/L, uncontrolled hypertension, AF with rate > 90/min, recent ACS, restrictive, infiltrative, or hypertrophic cardiomyopathy

Rationale and design: (A. Desai, Am Heart J 2011)

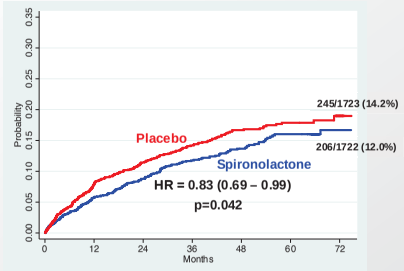
1°Outcome
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

TOPCAT Funded by the NHLBI



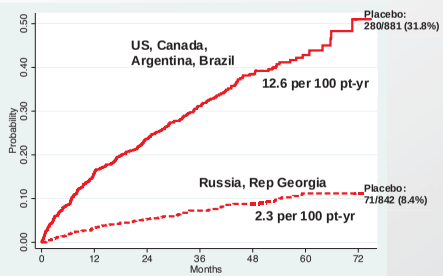
Heart Failure Hospitalizations

TOPCAT Funded by the NHLBI



Placebo Rates:
Primary Outcome, by region

TOPCAT Funded by the NHLBI



Subgroups

TOPCAT Funded by the NHLBI

Of 22 pre-specified, only 1 - Stratum - showed a significant interaction with treatment

Enrolled by:	Spiro	Placebo	Hazard Ratio (95% CI) P-value
Natriuretic peptide	78/490 (15.9%)	116/491 (23.6%)	**0.65** (0.49-0.87) **0.003**
Heart Failure Hosp	242/1232 (19.6%)	235/1232 (19.1%)	**1.01** (0.84-1.21) **0.923**

***P=0.013 for interaction**

HF-PEF Recommendation

Recommendation

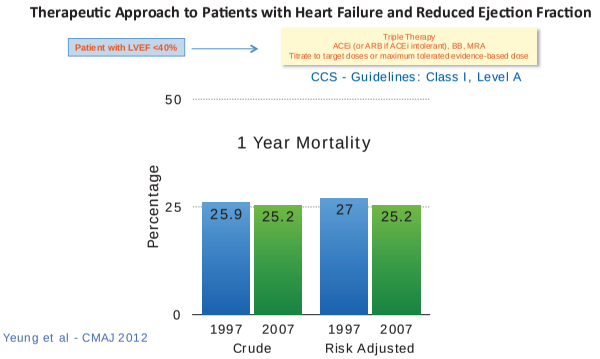
We suggest that in individuals with HFpEF, an increased NP level, serum potassium < 5.0 mmol/L, and an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min, a mineralocorticoid receptor antagonist like spironolactone should be considered, with close surveillance of serum potassium and creatinine (Weak Recommendation, Low-Quality Evidence).

Values and Preferences:
This recommendation is based on a prespecified subgroup analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, which includes analysis of the predefined outcomes according to admission NT-proBNP level, and the corroborating portion of the trial conducted within North and South America.

Moe GW, Ezekowitz JA et al., *Can J Cardiol*

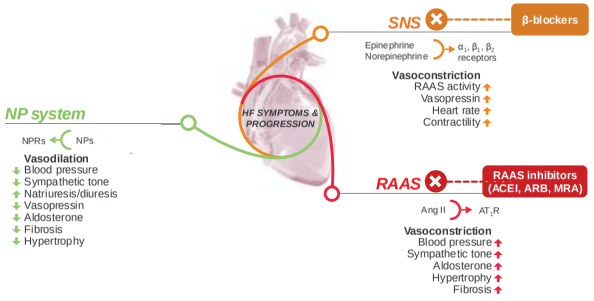
www.ccs.ca Heart Failure Guidelines

Heart Failure Prognosis - Ontario

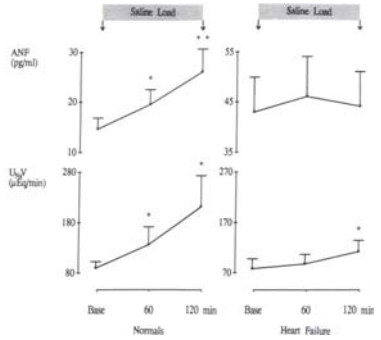


Yeung et al - CMAJ 2012

Neurohormonal Activation in HF

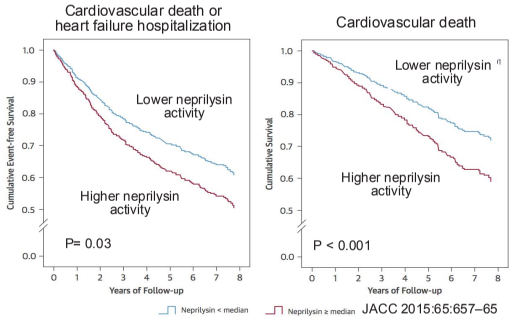


HF: A State of Relative Natriuretic Peptide Deficiency



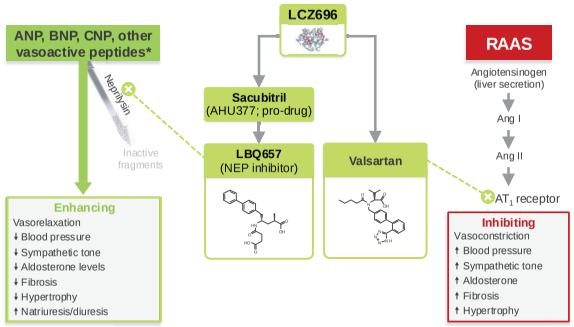
Volpe M et al, JCI 1991

Neprilysin in Heart Failure



JACC 2015:65:657–65

Neprilysin Inhibition



PARADIGM-HF: 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)

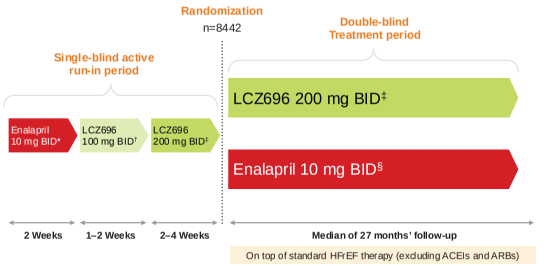
McMurray et al. N Engl J Med 2014;371:993–1004

PARADIGM-HF: Exclusion Criteria

- History of angioedema
- eGFR <30 mL/min/1.73 m^2 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

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

PARADIGM-HF: Study Design



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

PARADIGM-HF: Drop out

2079 (19.8%) Dropped out during the run-in phase

Hypotension, Renal dysfunction, and Hyperkalemia

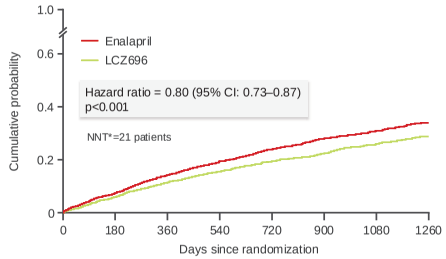
Parameter	OR (CI)
eGFR < 60 ml/min/1.73m2	1.49 (1.35 -1.65)
NT-proBNP (per log increment)	1.20 (1.14 -1.26)
SBP (per 10 mmHg decrease)	1.11 (1.07 - 1.14)
Ischemic Etiology	1.24 (1.13 - 1.39)

Desai et al, ESC 2015 Poster Presentation

PARADIGM-HF

Primary endpoint:

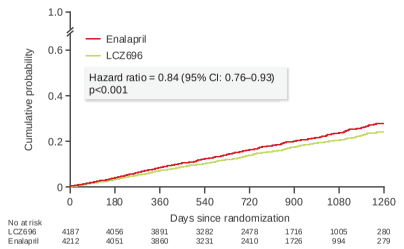
Death from CV causes or first hospitalization for HF



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

PARADIGM-HF

Death from any cause



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

PARADIGM-HF

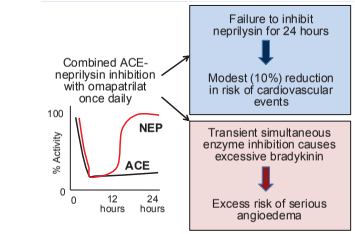
Prospectively defined safety events

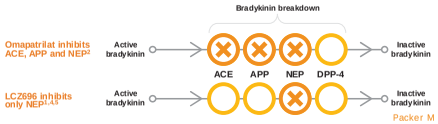
Event, n (%)	LCZ696 (n=4187)	Enalapril (n=4212)	p-value‡
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with SBP <90 mmHg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dL	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dL	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 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 (10.7 vs 12.3%, p=0.03)

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

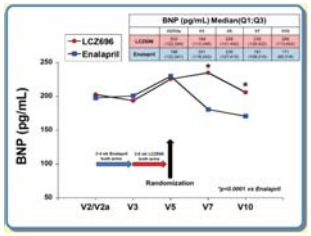
LCZ696 vs. Omapatrilat

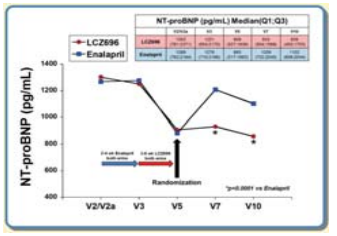




Packer M - ESC 2015 Presentation

PARADIGM-HF : Impact on NT-proBNP & Prognosis





Zile et al - HFSA 2015 Presentation

Canadian Cardiovascular Society HF Guidelines

HF – Reduced Ejection Fraction

Recommendation

We recommend that in patient with mild to moderate HF, an EF<35%, an elevated natriuretic peptide level or hospitalization for HF in the last 12 months, a serum potassium <5.2 mmol/L and an eGFR≥30 ml/min and treated with appropriate doses of guideline-directed medical therapy should be treated with LCZ696 in place of an ACE inhibitor or an ARB, with close surveillance of serum potassium and creatinine.

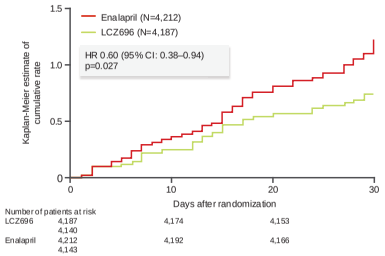
- Conditional Recommendation High Quality Evidence

Values and Preferences

This recommendation places high value on medication proven in large trials to reduce mortality, HF rehospitalization and symptom. It also considers the health economic implications of new medications. The recommendation is conditional because the drug is not yet approved for clinical use in Canada and the price is still not known.

PARADIGM-HF

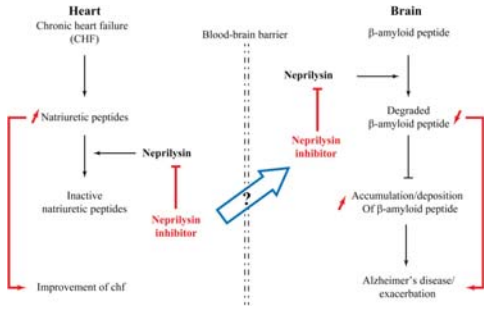
The reduction in heart failure hospitalization with LCZ696 was evident within the first 30 days after randomization



Contraindications

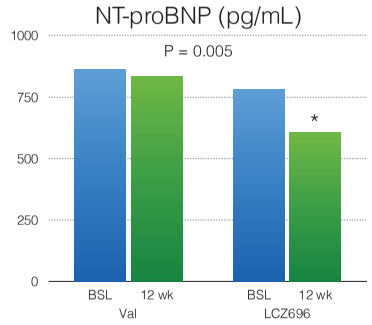
- Recent symptomatic hypotension prior to initiation of treatment with sacubitril/valsartan.
- Concomitant use with any drug formulation containing an angiotensin-converting enzyme inhibitor, due to potential enhanced risk of angioedema. Sacubitril/valsartan must not be administered until at least 36 hours have elapsed following discontinuation of ACEi therapy.
- Known history of angioedema related to previous ACEi or ARB therapy.
- History of hereditary or idiopathic angioedema.

Neprilysin Inhibition Potential Cognitive Effects

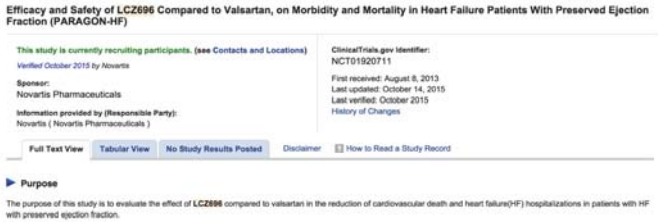


Vodovar et al, Eur Heart J 2015

PARAMOUNT Trial



Solomon S et al, Lancet 2012



Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF)

This study is currently recruiting participants. (see Contacts and Locations)
Verified October 2015 by Novartis

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01920711

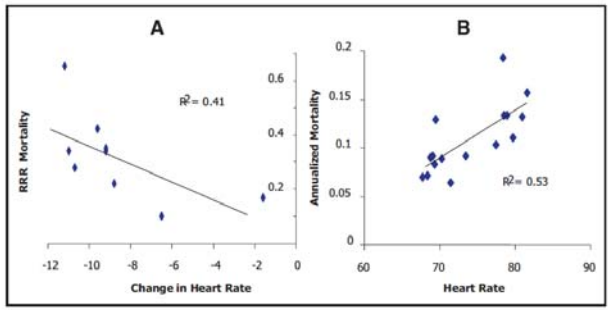
First received: August 8, 2013
Last updated: October 14, 2015
Last verified: October 2015
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

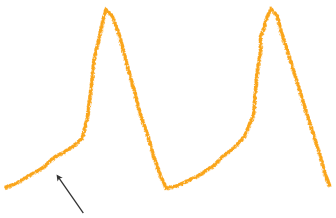
The purpose of this study is to evaluate the effect of **LCZ696** compared to valsartan in the reduction of cardiovascular death and heart failure(HF) hospitalizations in patients with HF with preserved ejection fraction.

Beta-Blockers: HR & Mortality



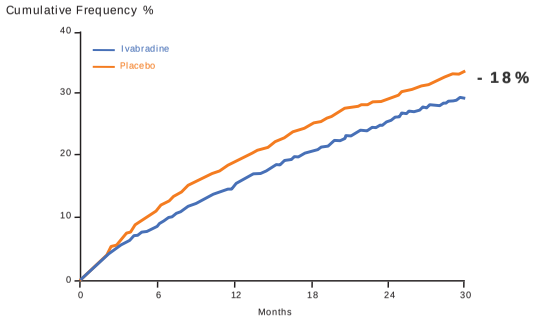
Flannery G, Gehrig-Mills R, Billah B, Krum H
American Journal of Cardiology - 2008, 101: 865-9

Sinus Node I_f Current - Ivabradine



- Funny Current
- Expressed in SN & Retina
- Blockade increases SV
- No effect on Contractility
- No effect on BP

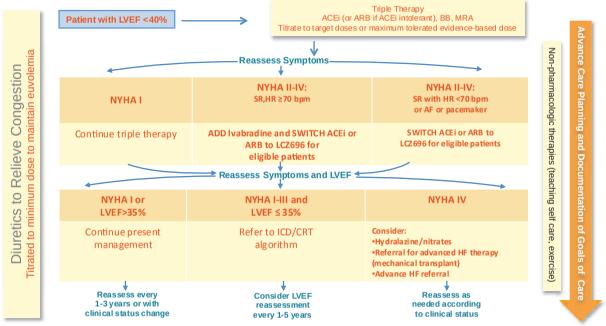
SHIFT Trial - MR + CV Hospitalization



Swedberg et al - Lancet 2010

CCS - HF Guideline

Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction



Heart Failure

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