9:45 – 10:45am

Managing Heart Failure In The PCP Setting

SPEAKER

Akshay S. Desai, MD, MPH

Presenter Disclosure Information

The following relationships exist related to this presentation:

- Akshay S. Desai, MD, MPH: Speakers Bureau for CardioMEMS; Relypsa Inc.; Novartis Pharmaceuticals Corporation; and St. Jude Medical. Consultant for CardioMEMS; Relypsa Inc.; Novartis Pharmaceuticals Corporation; and St. Jude Medical. Medical Advisory Board for Relypsa Inc. Clinical Trial Leadership for Novartis Pharmaceuticals Corporation.

Off-Label/Investigational Discussion

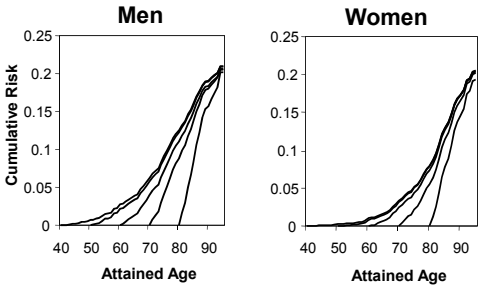
- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

The Next Frontier in Heart Failure: Where We've Come From and Where We are Going

Akshay S. Desai, MD, MPH
Associate Physician, Advanced Heart Disease Section
Cardiovascular Division
Brigham and Women's Hospital
Assistant Professor of Medicine
Harvard Medical School Boston, MA

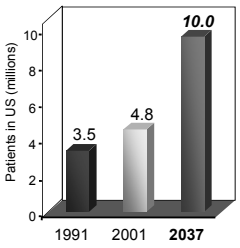
Why should we care about heart failure?

Lifetime Risk for CHF by Sex and Age



Lloyd-Jones et al. *Circulation*. 2002;106(24):3068-3072.

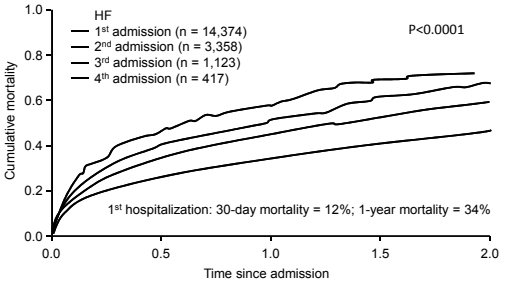
Heart Failure (HF): Scope of the Problem



- US prevalence*: 5.8 million
- US annual incidence: 670,000
- Annual mortality: 282,754
  - 5-10% depending on severity
- Cost: $39.2 billion
  - 53% of cost due to hospitalization

AHA Statistical Update. *Circulation*. 2010;121:e46-e215.
Croft JB et al. *J Am Geriatr Soc*. 1997;45:270–275. Rich M. *J Am Geriatric Soc*. 1997;45:968–974.

Mortality after HF Hospitalization



Setoguchi S, et al. *Am Heart J*. 2007;154:260-266.

Heart Failure Definition

- Pathophysiology: The inability to provide adequate cardiac output to the body at rest or with exertion, or to do so only in the setting of elevated cardiac filling pressures.

  -E. Braunwald modified by B. Borlaug and M. Redfield

- Clinically: A clinical syndrome characterized by breathlessness, fatigue and edema caused by an abnormality of the heart

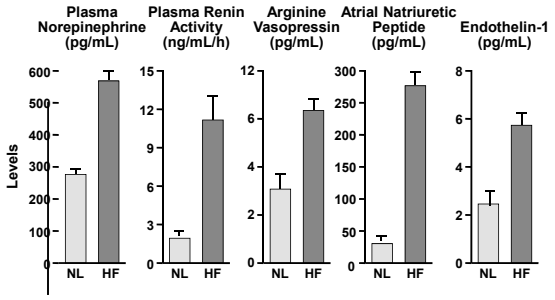
Heart Failure Symptoms

- Dyspnea
- Orthopnea
  - Number of pillows
- Cough
- GI Effects
  - Nausea, early satiety
- Fatigue
  - Reduced perfusion to skeletal muscles
- Peripheral edema
- CNS effects
  - Confusion, hallucinations
- Extremity effects
  - Cool extremities
- Urinary effects
  - Polyuria, nocturia

Treatment of Heart Failure

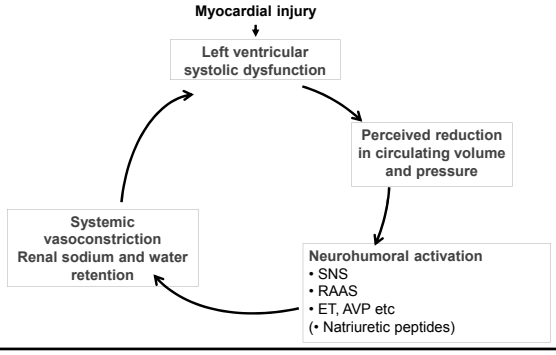
Empiric and Evidence-Based

Neurohormonal Activation in Heart Failure



Adapted from Cohn JN. Cardiology. 1997;88(suppl 2):2–6

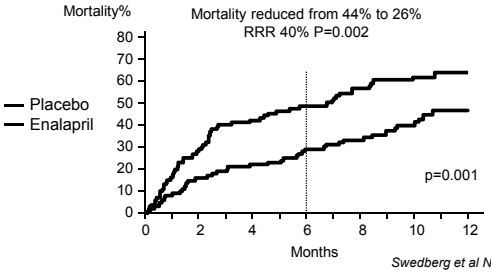
Pathophysiology



CONSENSUS

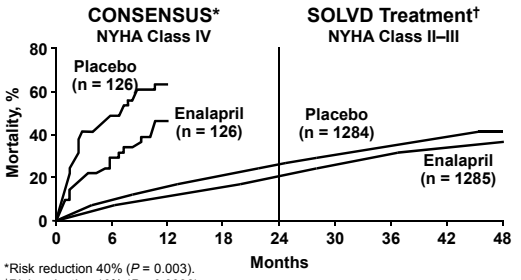
Co-operative North Scandinavian Survival Trial

253 patients, NYHA class IV only (no LVEF entry requirement). Furosemide 98% (mean dose 205mg), digoxin 93% and spironolactone 53% (mean dose 80mg). Mean follow-up 6.3 months.



Swedberg et al NEJM 1987

Effect of ACE inhibition in patients with CHF



*Risk reduction 40% (*P* = 0.003).
†Risk reduction 16% (*P* = 0.0036).

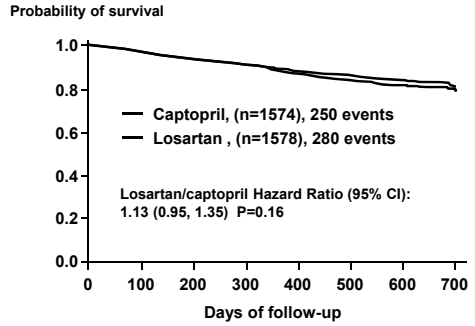
Swedberg K et al for the CONSENSUS Trial Study Group. *Circulation*. 1990;82:1730–1736.
The SOLVD Investigators. *N Engl J Med*. 1991;325:293–302.

HFSA 2010 Practice Guideline
ACE Inhibitors

Generic Name	Initial Daily Dose	Target Dose	Mean Dose in Clinical Trials
Captopril	6.25 mg tid	50 mg tid	122.7 mg/day
Enalapril	2.5 mg bid	10 mg bid	16.6 mg/day
Fosinopril	5-10 mg qd	80 mg qd	N/A
Lisinopril	2.5-5 mg qd	20 mg qd	4.5 mg/day, 33.2 mg/day*
Quinapril	5 mg bid	80 mg qd	N/A
Ramipril	1.25-2.5 mg qd	10 mg qd	N/A
Trandolapril	1 mg qd	4 mg qd	N/A

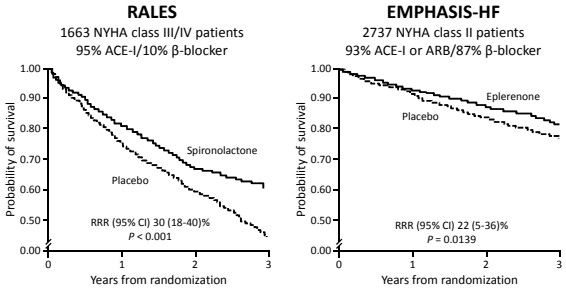
*No mortality difference between high and low dose groups, but 12% lower risk of death or hospitalization in high dose group vs. low dose group.

Losartan Heart Failure Survival Study: ELITE II
Primary Endpoint – All-Cause Mortality



Pitt et al Lancet. 2000; 355: 1582-7

Trials comparing an aldosterone/MR antagonist to placebo (added to an ACE inhibitor) in systolic HF



Pitt B, et al. *N Engl J Med*. 1999;341:709-717.

Zannad F, et al. *N Engl J Med*. 2010;364:11-21.

Aldosterone Antagonists: Doses

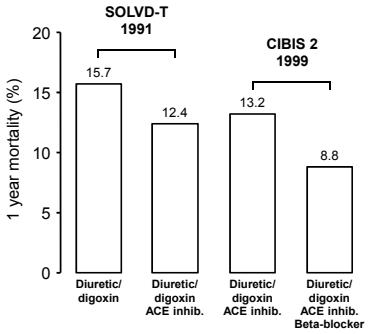
Generic Name	Initial Daily Dose	Target Dose	Mean Dose in Clinical Trials
Spironolactone	12.5-25 mg qd	25 mg qd	26 mg/day
Eplerenone	25 mg qd	50 mg qd	42.6 mg/day

HFSA 2010 Practice Guideline
Beta Blockers

Generic Name	Initial Daily Dose	Target Dose	Mean Dose in Clinical Trials
Bisoprolol	1.25 mg qd	10 mg qd	8.6 mg/day
Carvedilol	3.125 mg bid	25 mg bid	37 mg/day
Carvedilol	10 mg qd	80 mg qd	
Metoprolol succinate CR/XL	12.5-25 mg qd	200 mg qd	159 mg/day

Clinical Tidbits:
- ACE inhibitor first, to lower end of target range
- Beta blocker at LOW dose, titrate to target or maximum tolerated dose
- Go back to titrate ACE inhibitor to maximum dose

The stunning success of ACE inhibitors and beta blockers in mild-moderate HF

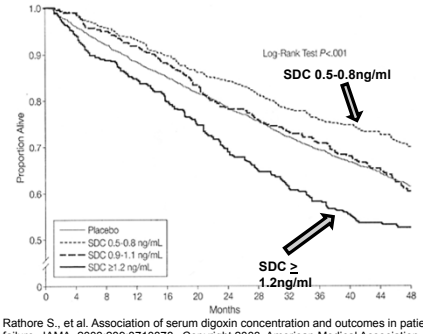


Digitalis Glycosides: Digoxin

Mechanism of action

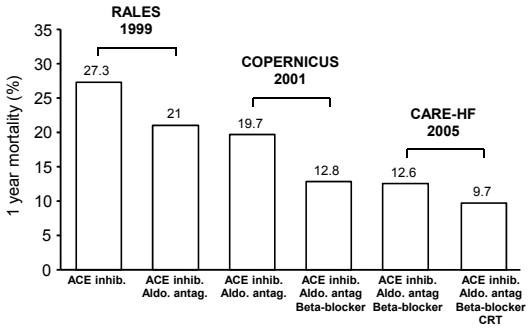
Inhibits Na^+-K^+ ATPase pump in
- Cardiac cells
- Non-cardiac cells
- Renal cells

DIG Trial: Survival Analysis Based on Serum Drug Concentration



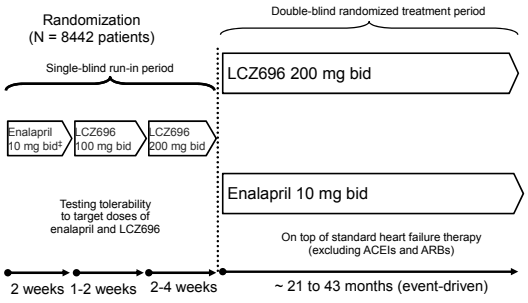
Rathore S., et al. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA. 2003;289:8710878. Copyright 2003. American Medical Association. All rights reserved.

Cumulative benefit of poly-pharmacy (and CRT) in severe HF



McMurray, et al. Eur J HF 2013

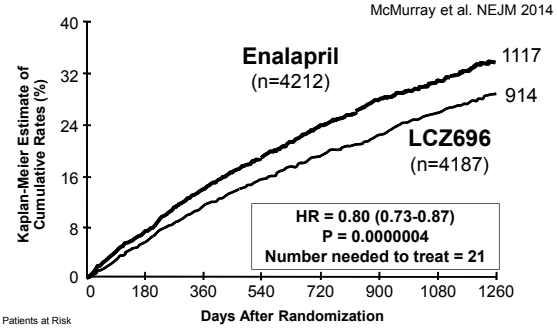
PARADIGM-HF: Study Design



‡ Enalapril 5 mg bid for 1-2 weeks followed by enalapril 10 mg bid as an optional starting run-in dose for those pts who are treated with ARBs or with low dose of ACEI

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

McMurray et al. NEJM 2014

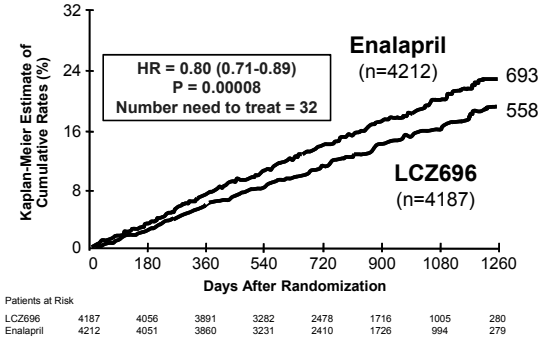


Patients at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

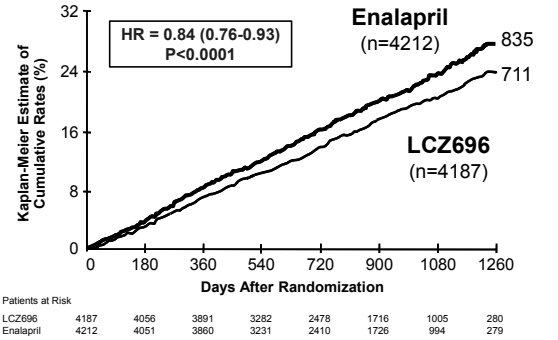
Cardiovascular Death

McMurray et al. NEJM 2014



PARADIGM-HF: All-Cause Mortality

McMurray et al. NEJM 2014

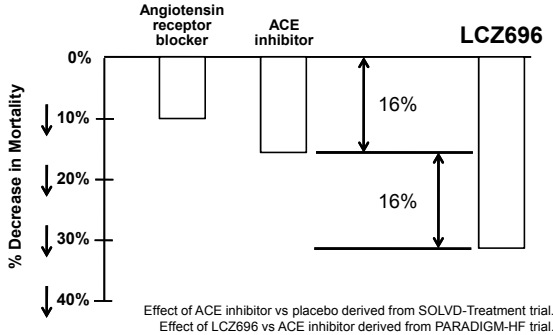


PARADIGM-HF: Adverse Events

McMurray et al. NEJM 2014

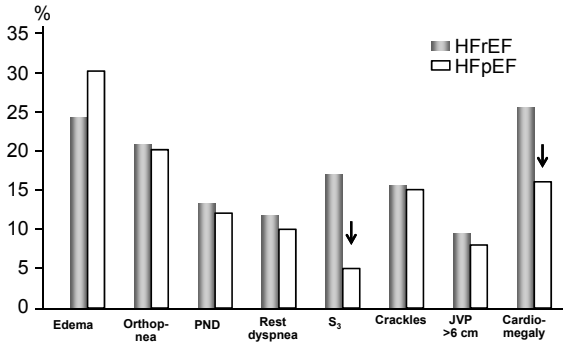
	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine > 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

LCZ696 Doubled the Survival Benefits of Current Renin-Angiotensin Inhibitors



Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial.
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial.

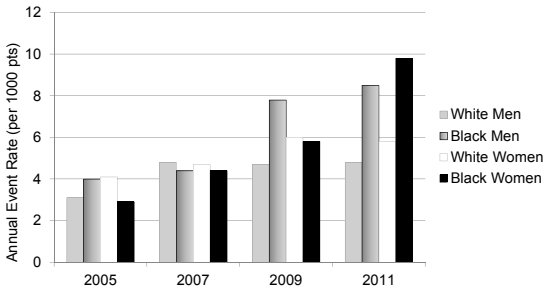
Similar Signs and Symptoms in Patients with HFpEF and HFrEF



CHARM Investigators

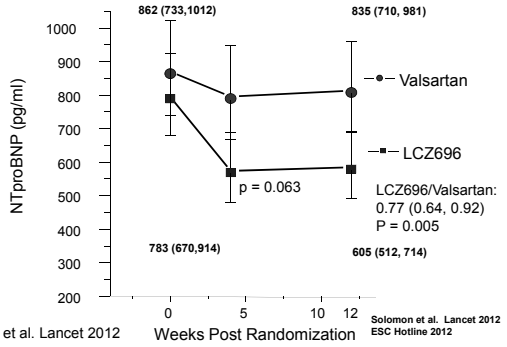
Acute HFpEF Admissions 2005-2011

Minneapolis, MD – Hagerstown, MD– Forsyth, NC - Jackson, MS



Rosemond. ARIC 2013 Unpublished

PARAMOUNT: Significant Reduction in NT-proBNP with LCZ696 at 12 Weeks



Solomon et al. Lancet 2012

Solomon et al. Lancet 2012
ESC Hotline 2012

PARAGON-HF: Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejectioN fraction

A randomized, double blind, trial to evaluate the long-term efficacy and safety profile of the angiotensin receptor neprilysin inhibitor (ARNI), LCZ696, compared with valsartan, in patients with heart failure with preserved ejection fraction (HFpEF)

Summary

- Heart failure remains extremely morbid and deadly
- Current treatment of HFrEF is both empiric (diuretics, lifestyle) and evidenced-based (ACEi, ARBs, Beta-Blockers, MRAs)
- Devices used for specific subsets (ICD for reduced EF, CRT for reduced EF and wide QRS/LBBB, LVAD for end-stage or bridge to transplant)
- New Therapies are likely to be approved for use soon based on results of recent clinical trials
- In HFpEF, current treatment remains empiric, with some evidence that RAAS blockade can be useful in some patients
- Clinical trials in HFpEF are ongoing with novel agents