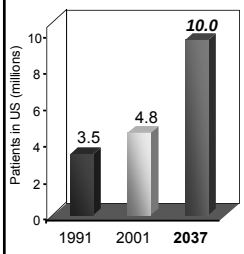
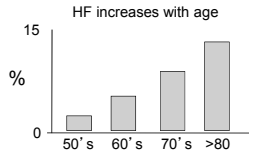
Heart Failure (HF): Scope of the Problem

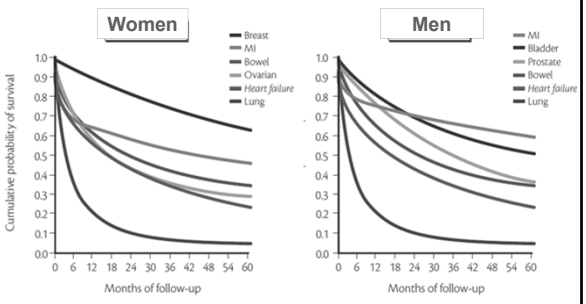


- US prevalence*: 5.8 million
- US annual incidence: 670,000
- Annual mortality: 282,754
  - 5-10% depending on severity
- Cost: $39.2 billion
  - 53% of cost due to hospitalization

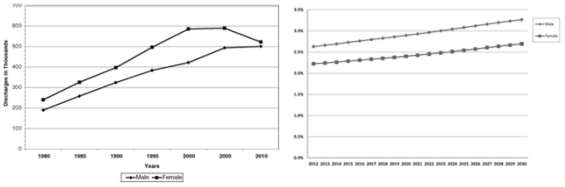


AHA Statistical Update. *Circulation.* 2010;121:e46-e215.
Croft JB et al. *J Am Geriatr Soc.* 1997;45:270–275. Rich M. *J Am Geriatric Soc*. 1997;45:968–974.

More malignant than cancer



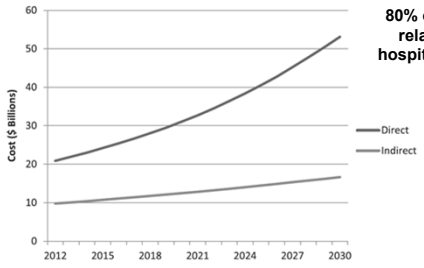
Hospital discharges for heart failure by sex in United States: 1980–2010 and Projected



Go A S et al. Circulation. 2013;127:e6-e245

Heidenreich P, et al. Circ Heart Fail 2013.

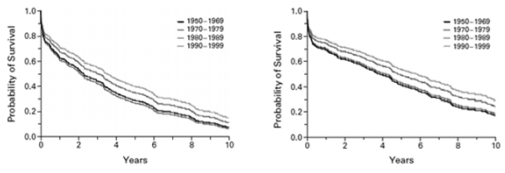
Projected Costs of Heart Failure Care



80% of costs related to hospitalization

Heidenreich P, et al. *Circ Heart Fail.* 2013.

Temporal Trends in Age-Adjusted Survival After HF Diagnosis



Men **Women**

Levy D, et al. *N Engl J Med.* 2002;347:1397-1402.

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

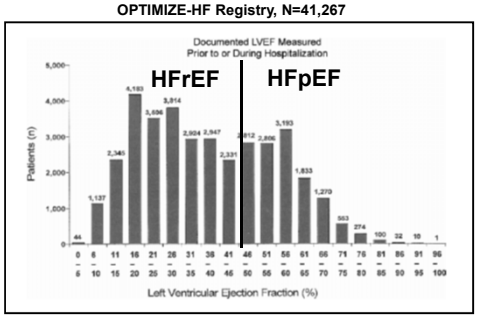
- Dyspnea
- Orthopnea
  - Number of pillows
- Cough
- GI Effects
  - Nausea, early satiety
- Fatigue
  - Reduced perfusion to skeletal muscles
- Peripheral edema
- CNS effects
  - Confusion, hallucinations
- Extremity effects
  - Cool extremities
- Urinary effects
  - Polyuria, nocturia

Treatment of Heart Failure

Empiric and Evidence-Based

Heart Failure with Preserved Ejection Fraction (HFpEF) accounts for up to Half of Heart Failure

OPTIMIZE-HF Registry, N=41,267



Fonarow G et al. *JACC.* 2007; 50:768-777.

Chlorothiazide induced diuresis in a patient with CHF

CLINICAL EXPERIENCE WITH CHLOROTHIAZIDE

J. D. H. SLATER
M.A., M.B. Cantab., M.R.C.P.
MEDICAL REGISTRAR

J. D. N. NABARRO
M.D. Lond., F.R.C.P.
ASSISTANT PHYSICIAN

THE LANCET 18 JANUARY 1958

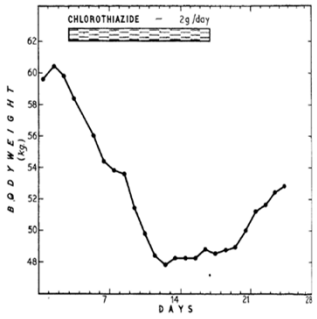
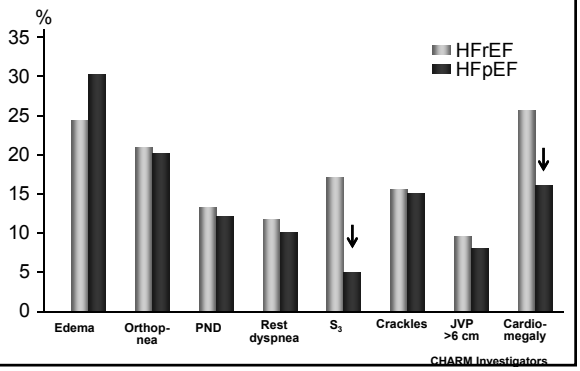


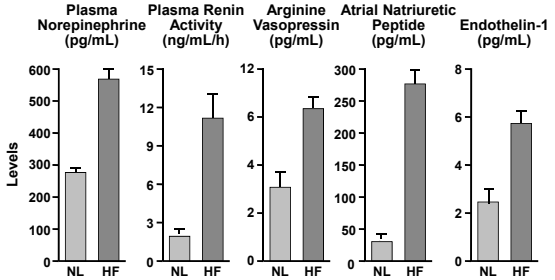
Fig. 6—Case 5 (congestive heart-failure): response of body-weight to first course of chlorothiazide.

Similar Signs and Symptoms in Patients with HFpEF and HFrEF



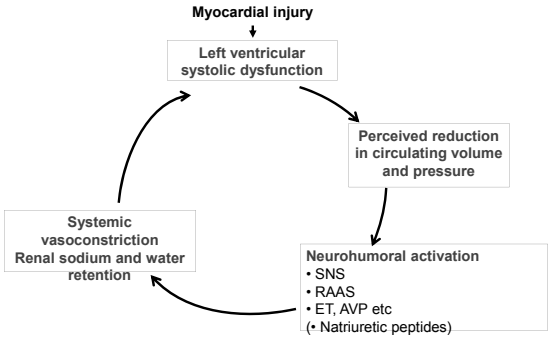
CHARM Investigators

Neurohormonal Activation in Heart Failure

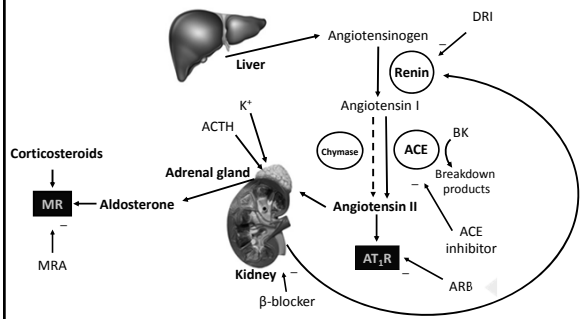


Adapted from Cohn JN. Cardiology. 1997;88(suppl 2):2–6

Pathophysiology

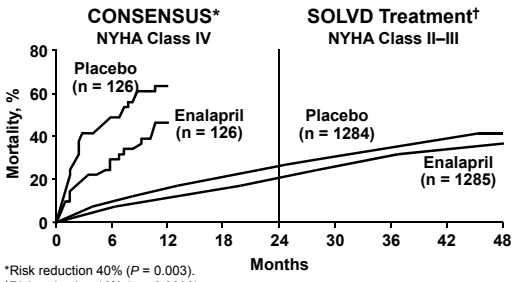


Is an ARB better than an ACE inhibitor?



DRI, direct renin inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; K^+ potassium ion; ACE, angiotensin converting enzyme; ACTH, adrenocorticotropic hormone (corticotropin); BK, bradykinin; AT_1R, angiotensin II type 1 receptor; MR, mineralcorticoid receptor

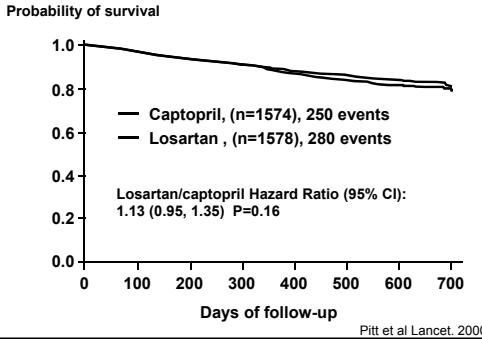
Effect of ACE inhibition in patients with CHF



*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.

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



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

HFSA 2010 Practice Guideline
ACE Inhibitors

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose in Clinical Trials
Captopril	Capoten	6.25 mg tid	50 mg tid	122.7 mg/day
Enalapril	Vasotec	2.5 mg bid	10 mg bid	16.6 mg/day
Fosinopril	Monopril	5-10 mg qd	80 mg qd	N/A
Lisinopril	Zestril, Prinivil	2.5-5 mg qd	20 mg qd	4.5 mg/day, 33.2 mg/day*
Quinapril	Accupril	5 mg bid	80 mg qd	N/A
Ramipril	Altace	1.25-2.5 mg qd	10 mg qd	N/A
Trandolapril	Mavik	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.

ARBs

- Class I: ARBs are recommended in patients with HFrEF with current or prior symptoms who are ACEI intolerant, unless contraindicated, to reduce morbidity and mortality

  Level of Evidence = A

- Class IIb: Addition of an ARB may be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACEI and a β-blocker in whom an aldosterone antagonist is not indicated or tolerated

  Level of Evidence = A

Routine combined use of an ACEI, ARB, and aldosterone receptor antagonist is potentially harmful for patients with HFrEF.

Level of Evidence = C

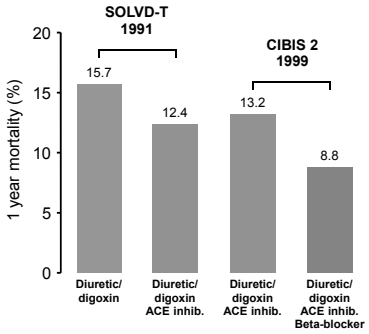
Circulation 2013;128:e240-327.

ARBs: Doses

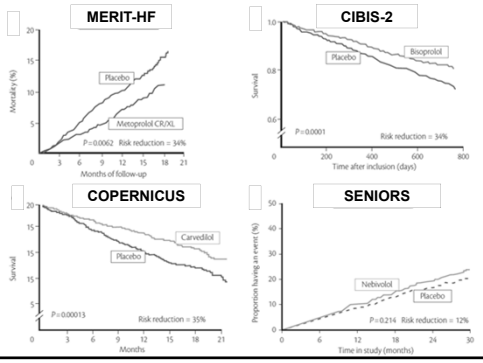
NOT a class effect, target doses used in clinical trials.

Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose in Clinical Trials
Candesartan	Atacand	4–8 mg QD	32 mg QD	24 mg/day
Losartan	Cozaar	12.5–25 mg QD	50–150 mg QD	129 mg/day
Valsartan	Diovan	40 mg BID	160 mg BID	254 mg/day

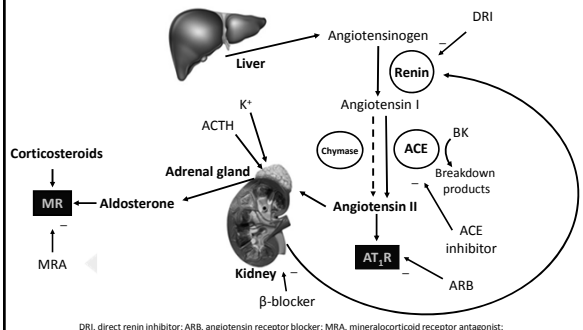
The stunning success of ACE inhibitors and beta blockers in mild-moderate HF



Beta-blockers are the most evidence-based therapy in heart failure



Is aldosterone (mineralocorticoid) antagonism beneficial in HF?



DRI, direct renin inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; K^+ potassium ion; ACE, angiotensin converting enzyme; ACTH, adrenocorticotropic hormone (corticotropin); BK, bradykinin; AT_1R, angiotensin II type 1 receptor; MR, mineralcorticoid receptor

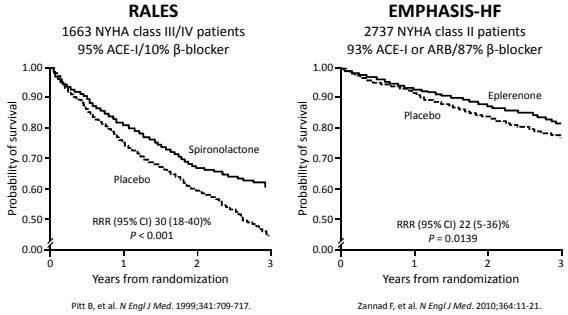
HFSA 2010 Practice Guideline Beta Blockers

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

Clinical Tidbits:

- ACEI first, to low doses
- β-Blocker at LOW dose; titrate to target or maximum tolerated dose
- Go back to titrate ACEI to target dose

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 Receptor Antagonists (ARAs or MRAs): ACCF/AHA Guidelines

- Aldosterone receptor antagonists (or MRAs) are recommended in patients with NYHA class II–IV and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality.

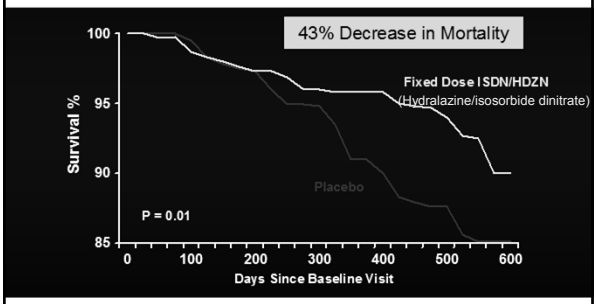
Strength of Evidence = A

- Aldosterone receptor antagonists are recommended to reduce morbidity and mortality after an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.

Strength of Evidence = B

Circulation 2013;128:e240-327.

A-HeFT All-Cause Mortality



Taylor AL. N Engl J Med 2004;351:2049-57.
Reprinted with permission from Massachusetts Medical Society.

Aldosterone Antagonists: Doses

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

Hydralazine and Isosorbide Dinitrate

- Class I: The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACEIs and β-blockers, unless contraindicated

Level of Evidence = A

- Class IIa: A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated

Level of Evidence = B

Circulation 2013;128:e240-327.

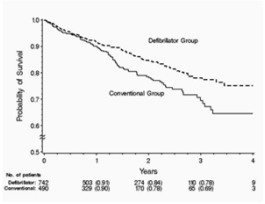
MRAs: Contraindications

- ***Not recommended when:***
  - ***creatinine is > 2.5 mg/dL (or creatinine clearance is < 30 mL/minute)***
  - ***or serum potassium is > 5.0 mmol/L***

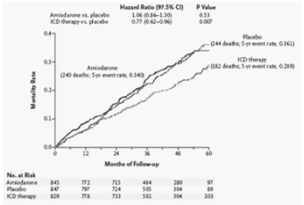
Level of Evidence = A

Circulation 2013;128:e240-327.

ICD Therapy in HF: MADIT-II and SCD-HeFT

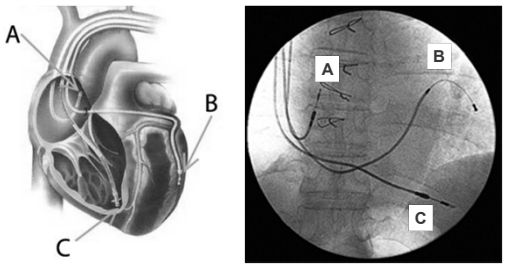


Moss et al, New Engl J Med 2002

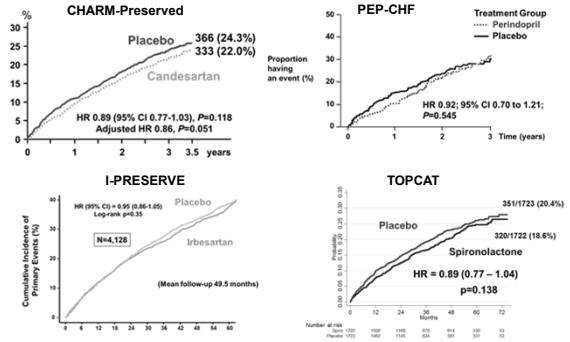


Bardy et al, New Engl J Med 2005

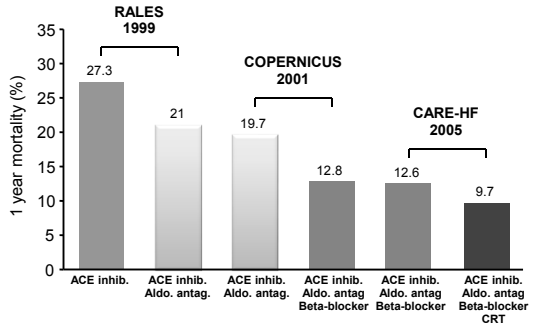
Biventricular/multi-site pacing or "cardiac resynchronization" therapy



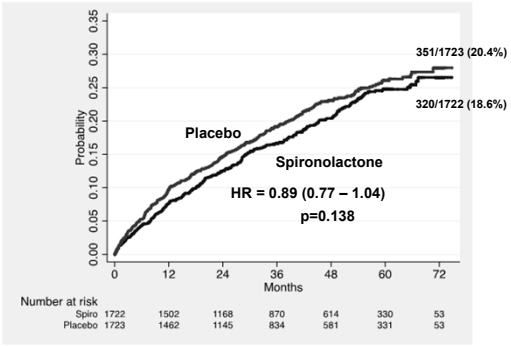
Outcomes Trials in HFpEF



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

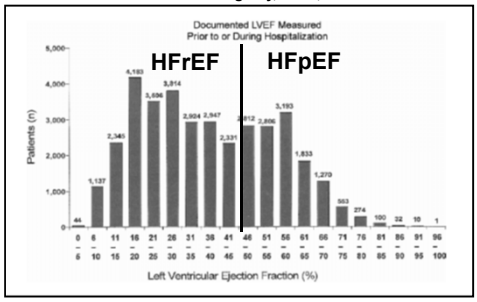


TOPCAT: 1°Outcome
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)



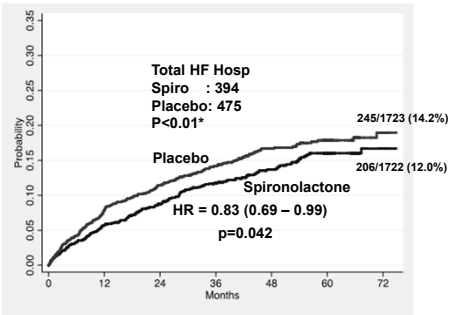
Heart Failure with Preserved Ejection Fraction (HFpEF) accounts for up to Half of Heart Failure

OPTIMIZE-HF Registry, N=41,267



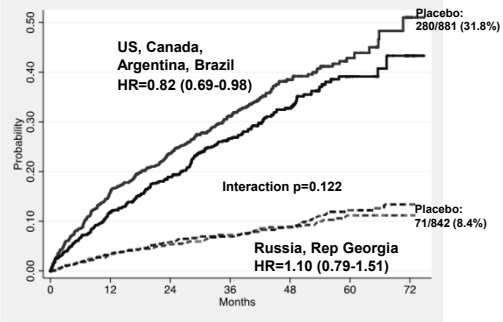
Fonarow G et al. *JACC*. 2007; 50:768-777.

TOPCAT: Heart Failure Hospitalizations

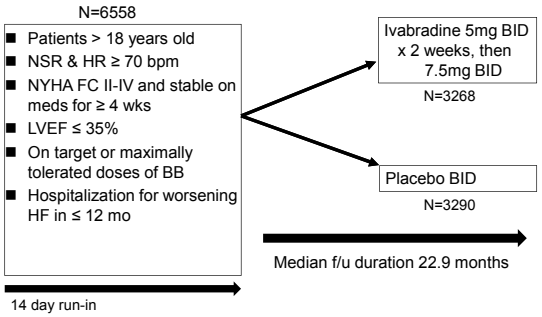


*poisson regression

Exploratory (post-hoc): Placebo vs. Spiro by region



SHIFT Study Design



Swedberg K. Lancet. 2010;376(9744):875-85.

2012 Update

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: John J. V. McMurray (Chairperson) (UK)*,

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF.
- Diuretics are used to control sodium and water retention and relieve breathlessness and oedema as in HF-REF.
- Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with AF

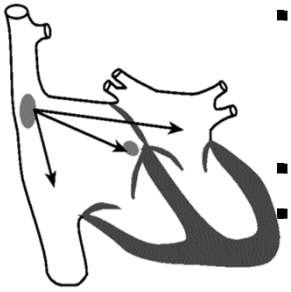
SHIFT Study Results

	Number of Events			
Outcome	Ivabradine	Placebo	HR (95% CI)	ARR
CV Death or HF Hospitalization	793	987	0.82 (0.75, 0.9)	4.2%
CV Death	449	491	0.91 (0.80, 1.03)	1.1%
HF Hospitalization	514	672	0.74 (0.66, 0.83)	4.7%

The treatment effect reflected only a reduction in the risk of hospitalization for worsening HF; there was no benefit observed for the mortality component of the primary endpoint

Swedberg K. Lancet. 2010;376(9744):875-85.

Sinus node inhibition with Ivabradine



- MOA: Blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel in the sinoatrial node, responsible for the I_f current
  - Delays diastolic depolarization
- Does not affect other ion channels
- Does not alter myocardial contractility and intra-cardiac conduction

Adverse Drug Reactions with Rates ≥ 1% on Ivabradine versus Placebo

Adverse Reaction	Ivabradine N=3260	Placebo N=3278
Bradycardia	10%	2.2%
Hypertension	8.9%	7.8%
Atrial Fibrillation	8.3%	6.6%
Phosphenes (visual brightness)*	2.8%	0.5%

*inhibition of the retinal current I_h, responsible for curtailing retinal responses to bright light stimuli. Most pronounced under triggering circumstances (rapid changes in brightness)

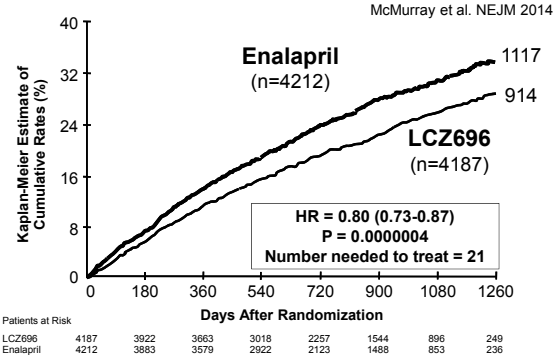
Swedberg K. Lancet. 2010;376(9744):875-85.

Ivabradine Considerations

- Indication: To reduce the risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF
  - LVEF ≤ 35%
  - In sinus rhythm with resting heart rate ≥ 70 beats/minute
  - Either on maximally tolerated doses of β-blockers or have a contraindication to β-blocker use
- Doses: Starting dose 5 mg twice daily, up to 7.5mg twice daily

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

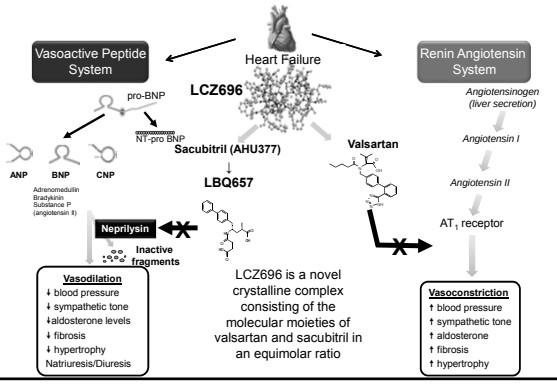
McMurray et al. NEJM 2014



Patients at Risk

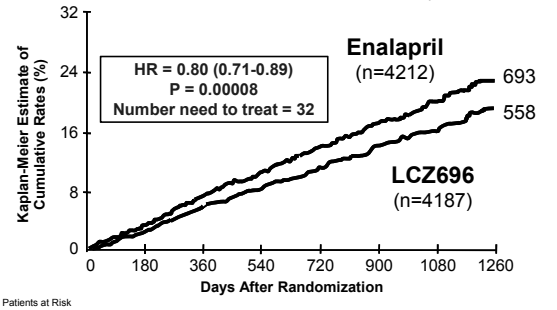
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

LCZ696 – A first-in-class Angiotensin Receptor Neprilysin Inhibitor – Simultaneously Inhibits NEP and the RAS



Cardiovascular Death

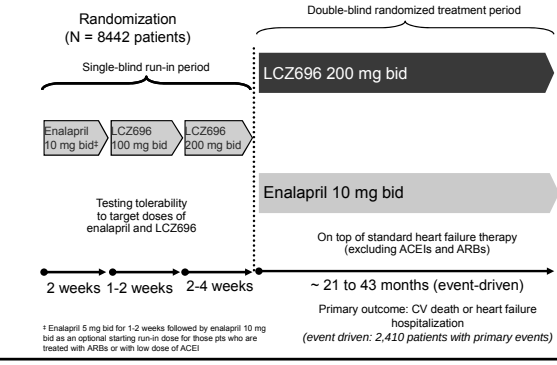
McMurray et al. NEJM 2014



Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

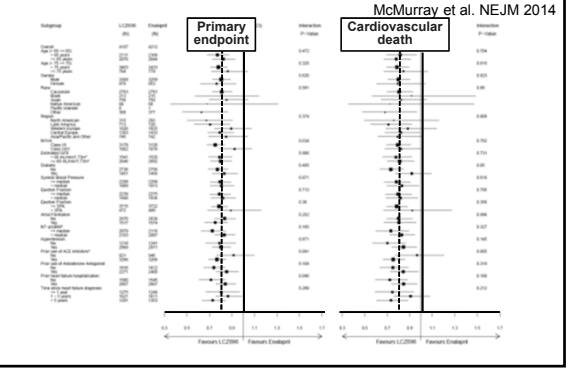
PARADIGM-HF: Study Design



‡ 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

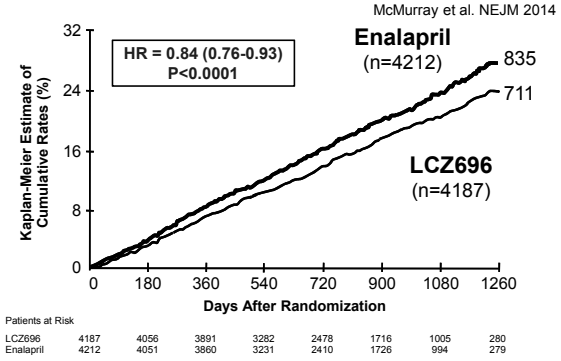
LCZ696 vs Enalapril on Primary Endpoint and on Cardiovascular Death, by Subgroups

McMurray et al. NEJM 2014



PARADIGM-HF: All-Cause Mortality

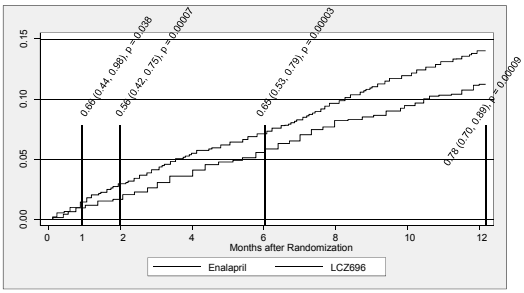
McMurray et al. NEJM 2014



Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

Early Benefit of LCZ696



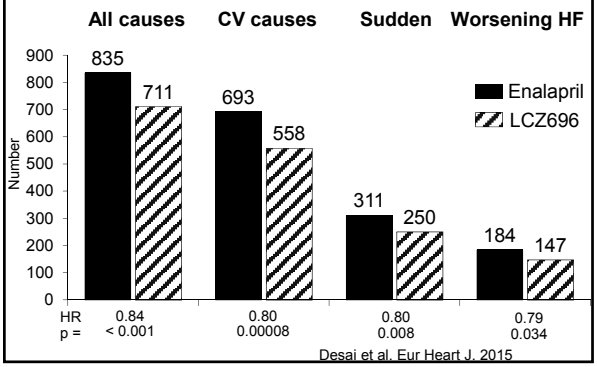
Packer et al. Circulation 2014

PARADIGM-HF: Adverse Events

McMurray et al. NEJM 2014

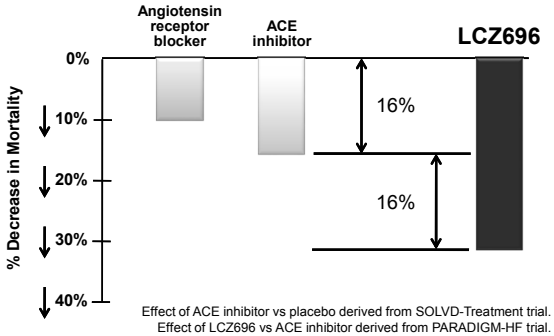
	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine > 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation 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	----

PARADIGM-HF: Mode of Death



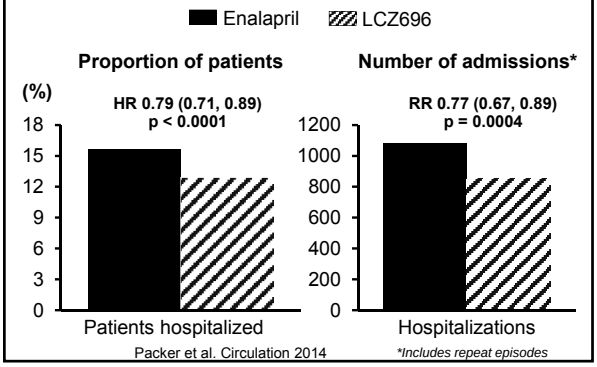
Desai et al. Eur Heart J. 2015

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.

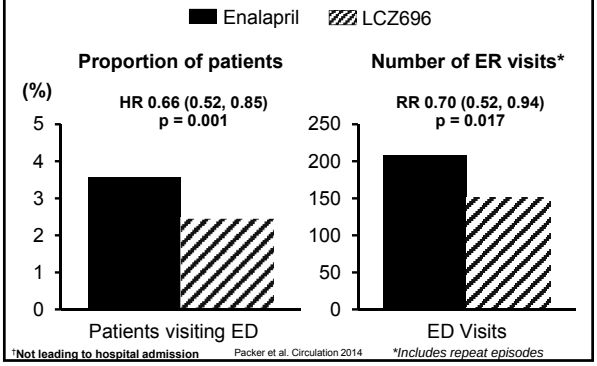
PARADIGM-HF: Hospitalization for heart failure



Packer et al. Circulation 2014

*Includes repeat episodes

PARADIGM-HF: Emergency department visits for heart failure†

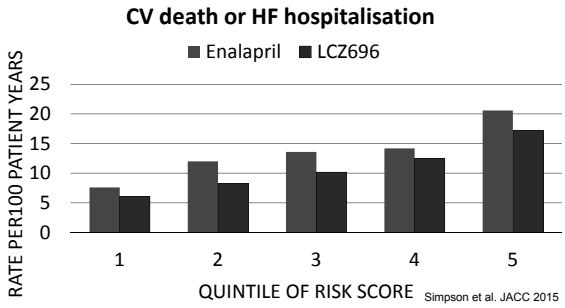


†Not leading to hospital admission

Packer et al. Circulation 2014

*Includes repeat episodes

LCZ Effective Across a Spectrum of Risk: The MAGGIC Risk Score



Simpson et al. JACC 2015

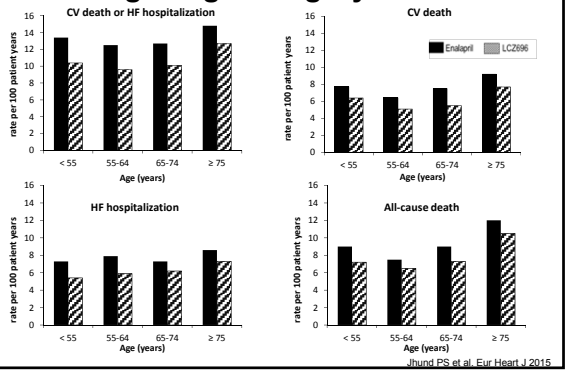
PARADIGM-HF: Intensive care management

Intensive management in hospital

	LCZ696 N=4187 n (%)	Enalapril N=4212 n (%)	P-value
Number of patients requiring intensive care	549 (13.1)	623 (14.8)	0.87 (0.78, 0.98) P=0.019
Total number of stays in intensive care	768	879	0.82 (0.72, 0.94) P=0.005
Patients receiving IV positive inotropic drugs	161 (3.8%)	229 (5.4%)	0.69 (0.57, 0.85) P < 0.001

Packer et al. Circulation 2014

PARADIGM-HF: Effect of LCZ696 according to age category

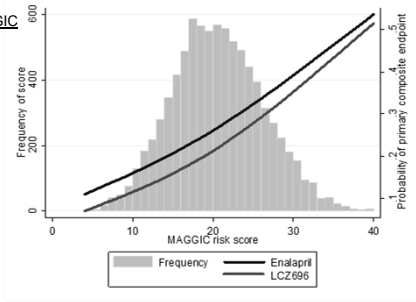


Jhund PS et al. Eur Heart J 2015

Is LCZ Effective Across the Spectrum of Heart Failure

Components of MAGGIC Score:

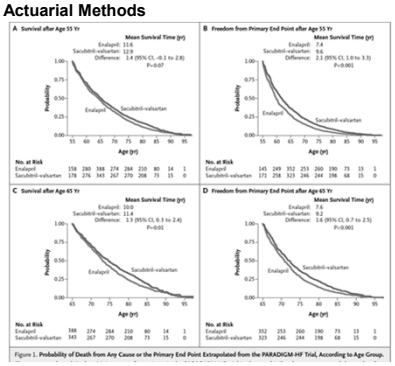
- Age
- SBP
- BMI
- Creatinine
- NYHA
- Sex
- Smoking
- DM
- COPD



Simpson et al. JACC 2015

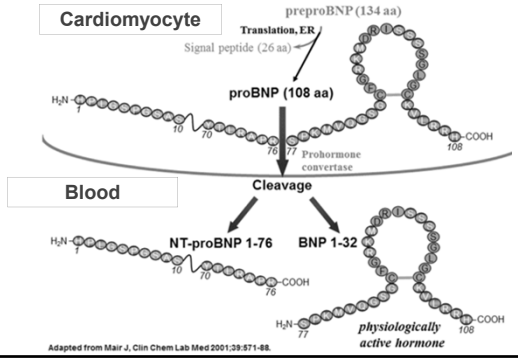
Estimated Long-Term Benefit at Various Ages

Using Actuarial Methods



Claggett et al. N Engl J Med 2015

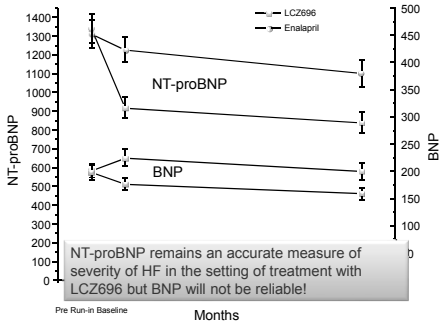
NT pro BNP and BNP



Sacubitril/Valsartan Considerations

- Indication: To reduce the risk of cardiovascular death and hospitalization for HF in patients with chronic heart failure (NYHA class II–IV) and reduced ejection fraction
  - Used in place of ACEI or ARB
- Doses: 24/26 mg, 49/51 mg, 97/103 mg
  - Starting dose 49/51 mg twice daily for patients previously on ACEI or ARB, 24/26 mg for low dose ACEI/ARB (</= 10mg enalapril daily) or ACEI/ARB naive
  - MUST have 36 hours washout between ACEI dose and sacubitril/valsartan initiation

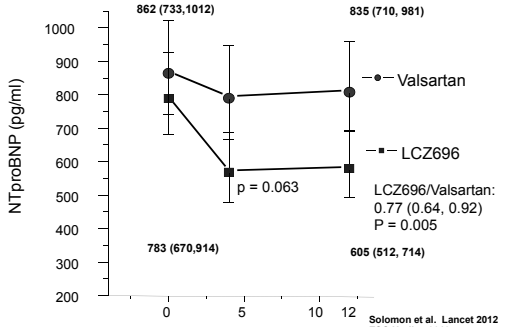
Mechanism: NT-proBNP and BNP



NT-proBNP remains an accurate measure of severity of HF in the setting of treatment with LCZ696 but BNP will not be reliable!

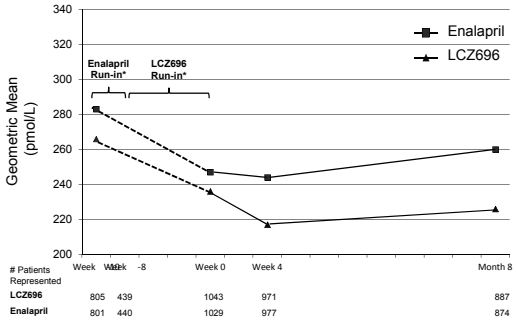
McMurray et al. NEJM 2014

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



Solomon et al. Lancet 2012

PARADIGM-HF: Effects of LCZ696 or Enalapril on hs-Troponin T in patients with HFrEF



Packer et al. Circulation 2014

PARAGONHF

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