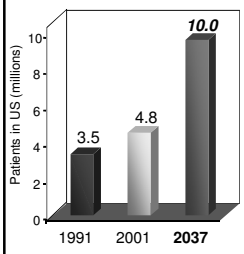
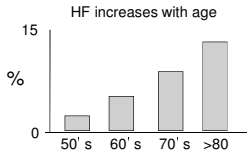
Heart Failure (HF): Scope of the Problem

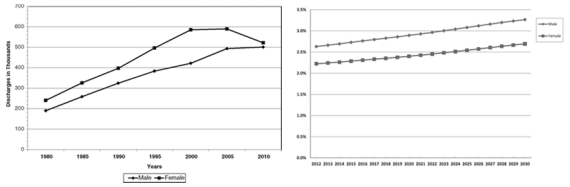


- US prevalence*: 5.8 million
- US annual incidence: 670,000
- Annual mortality: 282,754
  - 5-10% depending on severity
- Cost: $39.2 billion
  - 53% of cost due to hospitalization



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.

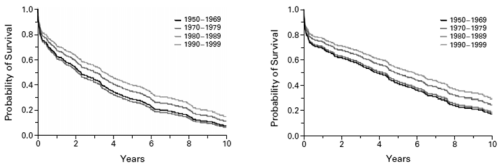
Hospital discharges for heart failure by sex in United States: 1980–2010 and Projected



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

Heidenreich P, et al. Circ Heart Fail 2013.

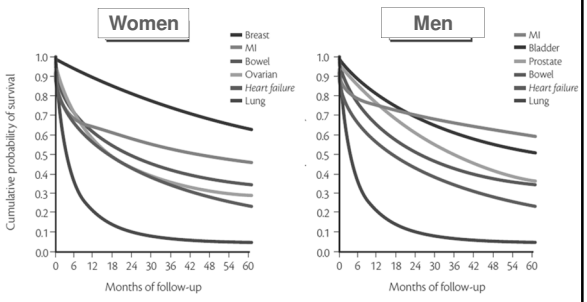
Temporal Trends in Age-Adjusted Survival After HF Diagnosis



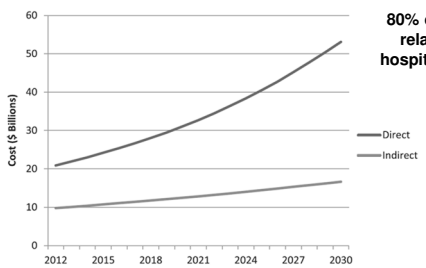
Men **Women**

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

More malignant than cancer



Projected Costs of Heart Failure Care



80% of costs related to hospitalization

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

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.

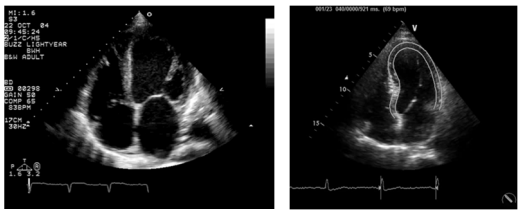
  -E. Braunwald modified by B. Borlaug and M. Redfield

- 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

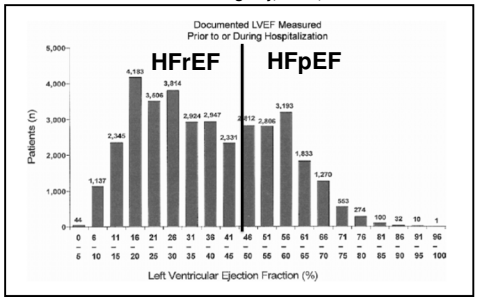
The Two Faces of Heart Failure



HFrEF HFpEF

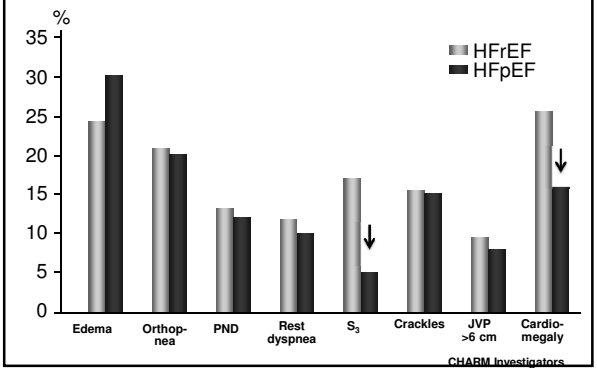
Heart Failure with Preserved Ejection Fraction (HFpEF) accounts for up to Half of Heart Failure

OPTIMIZE-HF Registry, N=41,267



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

Similar Signs and Symptoms in Patients with HFpEF and HFrEF



Treatment of Heart Failure

Empiric and Evidence-Based

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

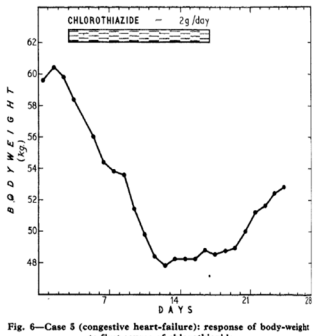
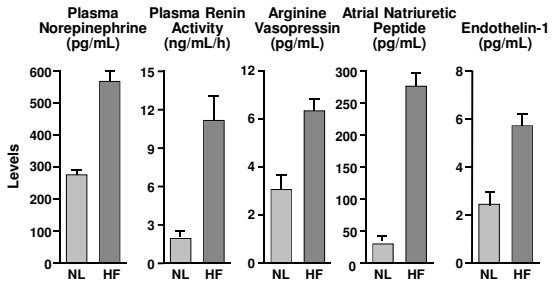


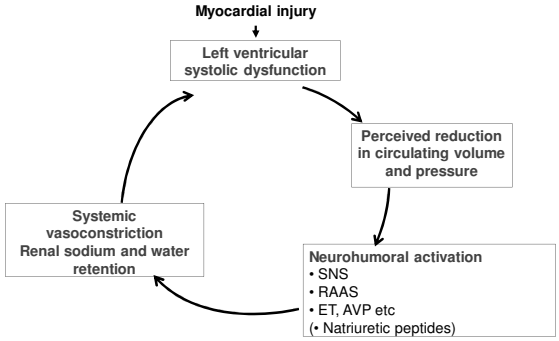
Fig. 6—Case 5 (congestive heart-failure): response of body-weight to first course of chlorothiazide.

Neurohormonal Activation in Heart Failure

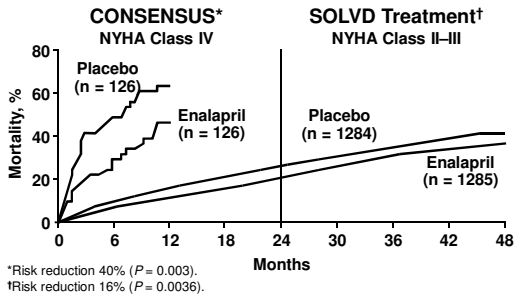


Adapted from Cohn JN. Cardiology. 1997;88(suppl 2):2–6

Pathophysiology



Effect of ACE inhibition in patients with CHF



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

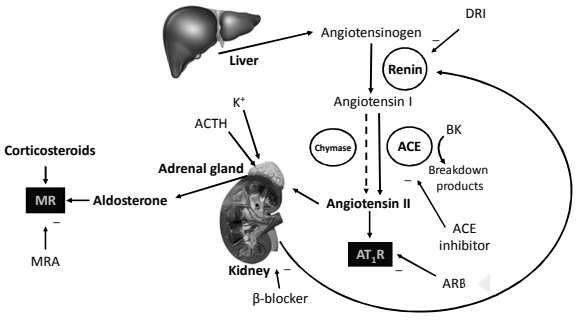
Swedberg K et al for the CONSENSUS Trial Study Group. *Circulation.* 1990;82:1730–1736.
The SOLVD Investigators. *N Engl J Med.* 1991;325:293–302.

ACCF/AHA Guideline for the Management of Heart Failure
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

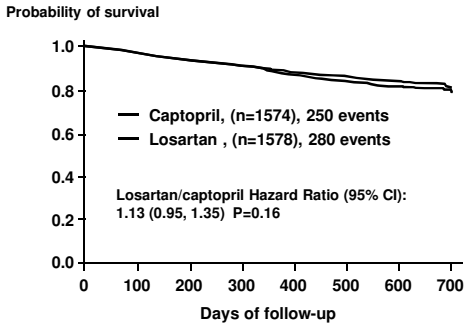
*No mortality difference between high and low dose groups, but 12% lower risk of death or hospitalization in high dose group vs. low dose group.

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

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



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

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
- 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

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 ACE inhibitors because of cough or angioedema (IA)

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

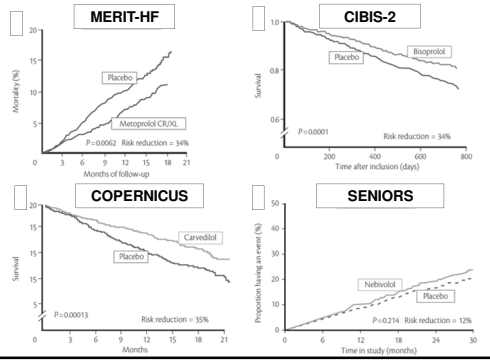
Circulation 2013;128:e240-327.

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

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

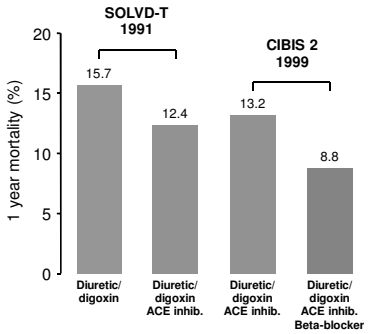


ACCF/AHA Guideline for the Management of Heart Failure
Beta Blockers

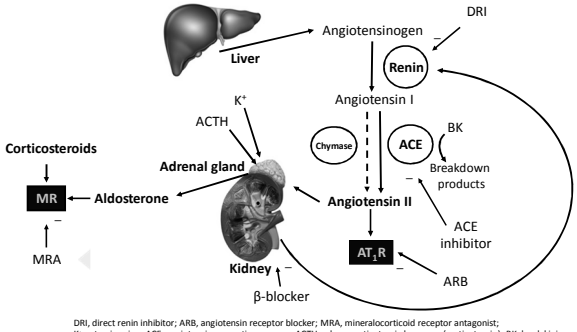
Generic Name	Trade Name	Initial Daily Dose	Target Dose	Mean Dose in Clinical Trials
Bisoprolol	**Zebeta**	**1.25 mg qd**	**10 mg qd**	**8.6 mg/day**
Carvedilol	**Coreg**	**3.125 mg bid**	**25 mg bid**	**37 mg/day**
Carvedilol	**Coreg CR**	**10 mg qd**	**80 mg qd**	
Metoprolol succinate CR/XL	**Toprol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

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

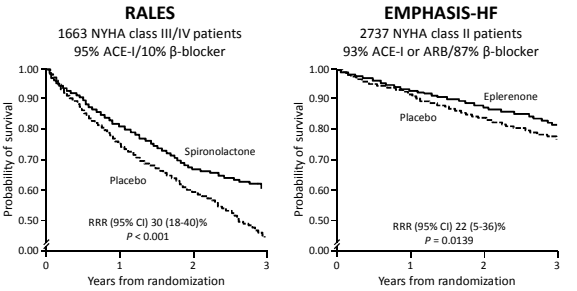


Is aldosterone (mineralocorticoid) antagonism beneficial in HF?



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

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.

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**

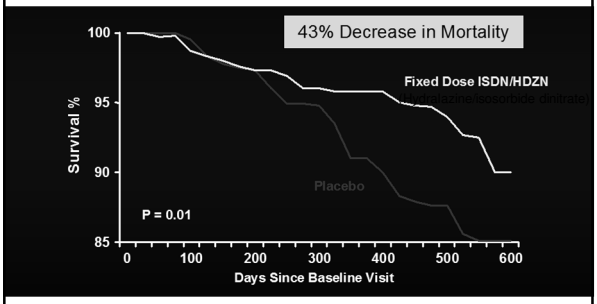
MRAs: Contraindications

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

Level of Evidence = A

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.

Hydralazine and Isosorbide Dinitrate

- <u>Class I</u>: 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

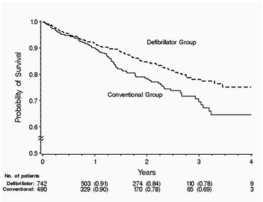
Level of Evidence = A

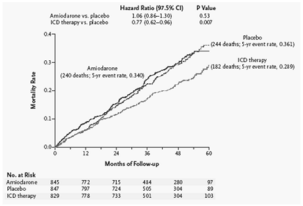
- <u>Class IIa</u>: A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated

Level of Evidence = B

Circulation 2013;128:e240-327.

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

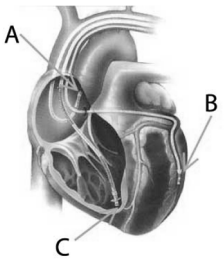


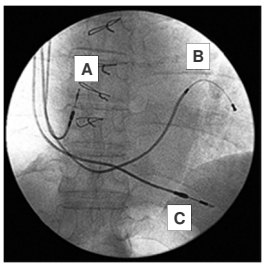


Moss et al, New Engl J Med 2002

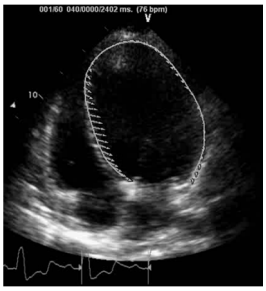
Bardy et al, New Engl J Med 2005

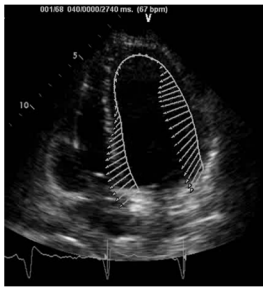
Biventricular/multi-site pacing or "cardiac resynchronization" therapy





CRT Improves Synchrony and Reverses Adverse Remodeling

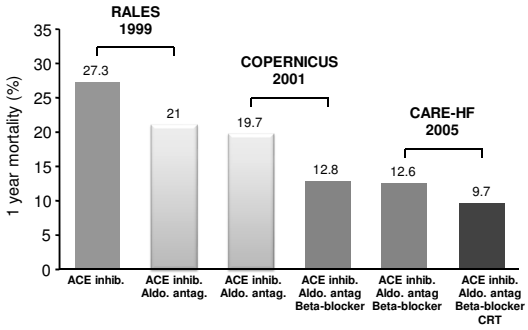




Baseline

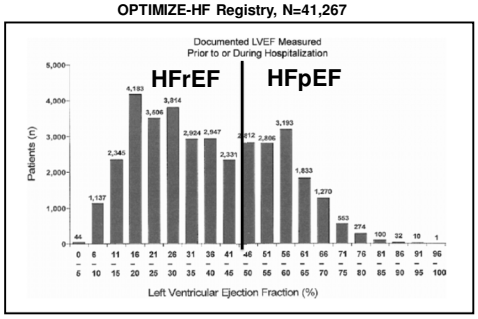
12 months CRT

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



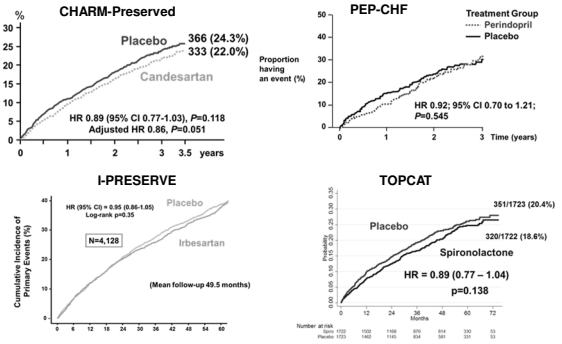
Heart Failure with Preserved Ejection Fraction (HFpEF) accounts for up to Half of Heart Failure

OPTIMIZE-HF Registry, N=41,267

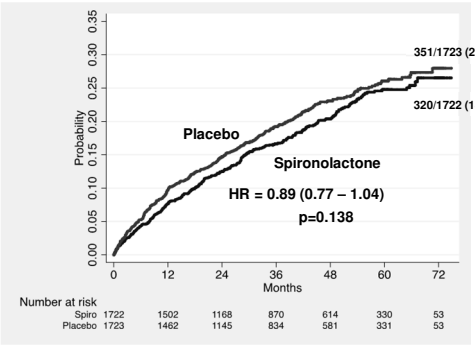


Fonarow G et al. *JACC.* 2007; 50:768-777.

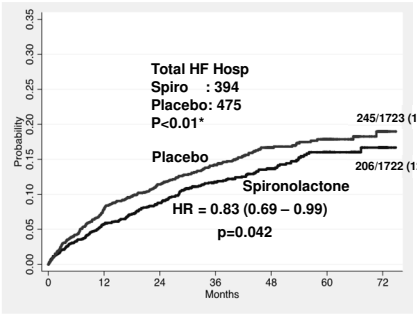
Outcomes Trials in HFpEF



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

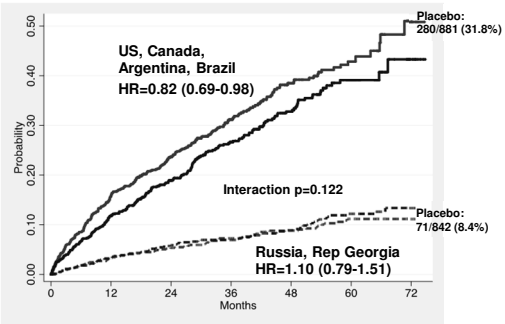


TOPCAT: Heart Failure Hospitalizations



*poisson regression

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



2016 Update

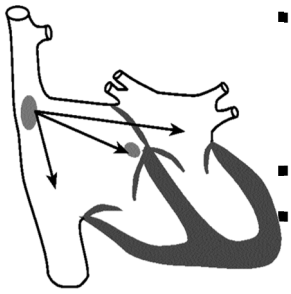
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFpEF.
- Diuretics are used to control sodium and water retention and relieve breathlessness and edema as in HFrEF.
- Adequate treatment of hypertension and myocardial ischemia is also considered to be important

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

SHIFT Study Design

N=6558

- Patients > 18 years old
- NSR & HR ≥ 70 bpm
- NYHA FC II-IV and stable on meds for ≥ 4 wks
- LVEF ≤ 35%
- On target or maximally tolerated doses of BB
- Hospitalization for worsening HF in ≤ 12 mo

Ivabradine 5mg BID x 2 weeks, then 7.5mg BID
N=3268

Placebo BID
N=3290

Median f/u duration 22.9 months

14 day run-in

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

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.

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.

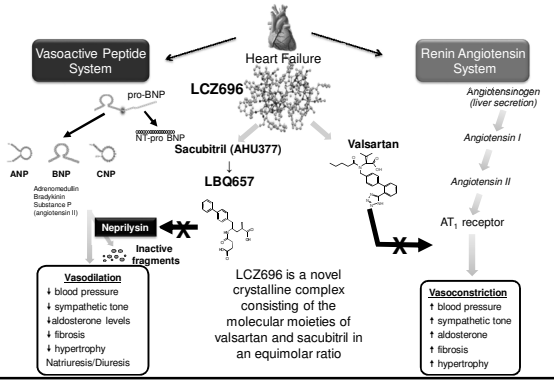
Ivabradine Considerations

- 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

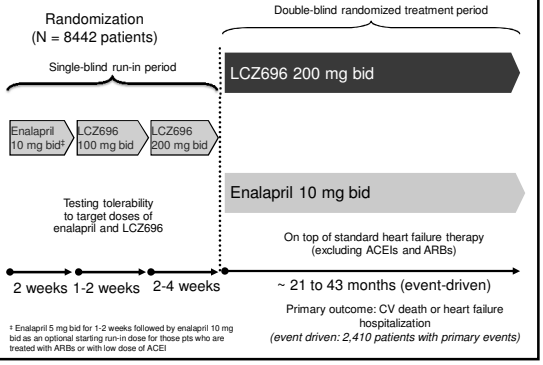
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

- **Ivabradine** can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (IIa, B-R)
  - Only 25% of patients studied in SHIFT were on optimal doses of beta-blocker therapy. It is important to initiate and up titrate these agents to target doses, as tolerated, before assessing the resting heart rate for consideration of ivabradine initiation

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

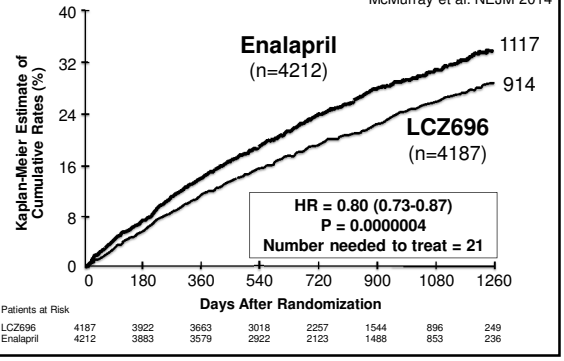


PARADIGM-HF: Study Design



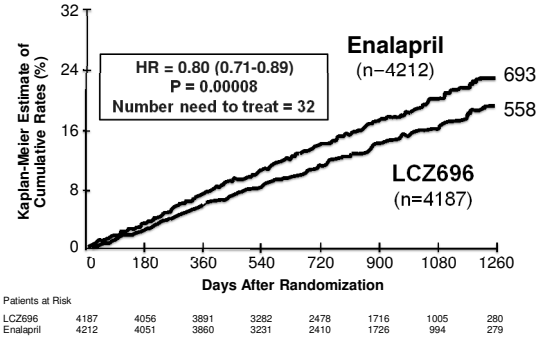
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

McMurray et al. NEJM 2014



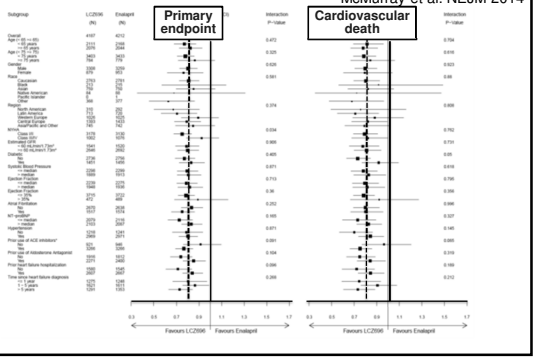
Cardiovascular Death

McMurray et al. NEJM 2014



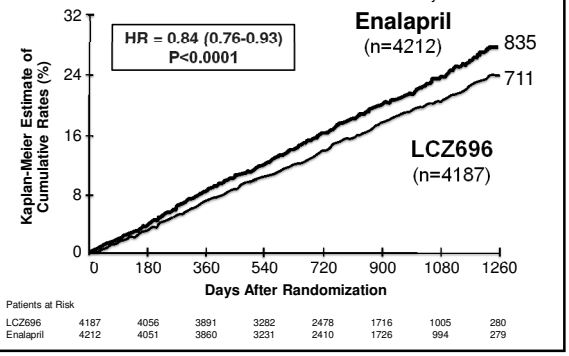
LCZ696 vs Enalapril on Primary Endpoint and on Cardiovascular Death, by Subgroups

McMurray et al. NEJM 2014



PARADIGM-HF: All-Cause Mortality

McMurray et al. NEJM 2014

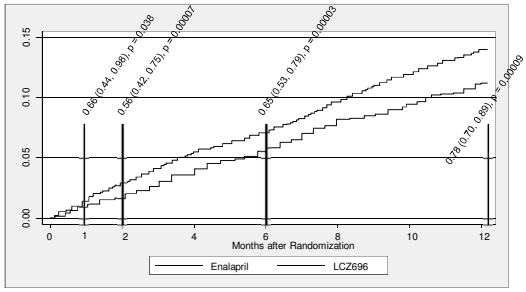


PARADIGM-HF: Adverse Events

McMurray et al. NEJM 2014

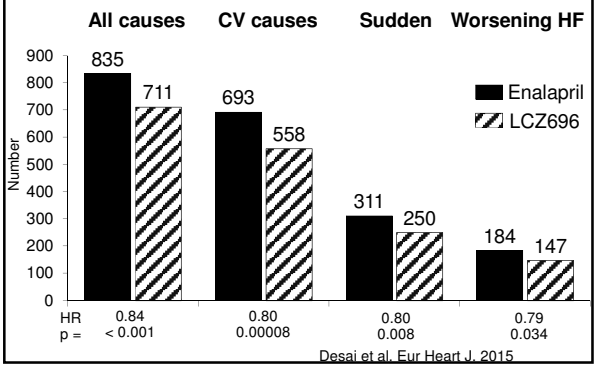
	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine > 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation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

Early Benefit of LCZ696



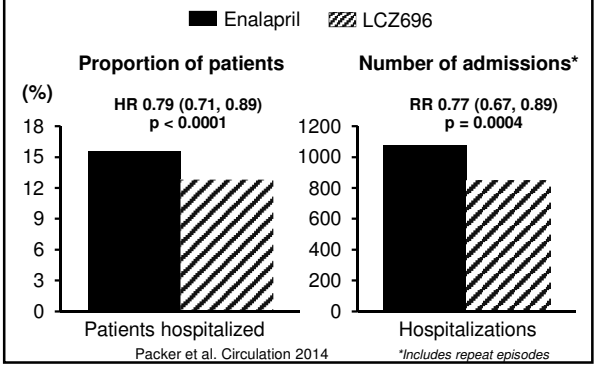
Packer et al. Circulation 2014

PARADIGM-HF: Mode of Death



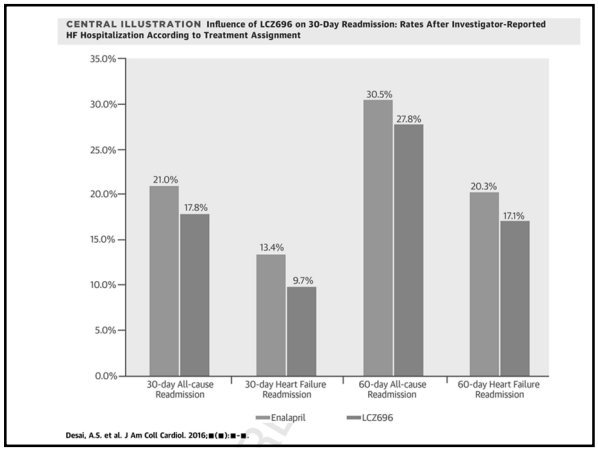
Desai et al. Eur Heart J. 2015

PARADIGM-HF: Hospitalization for heart failure

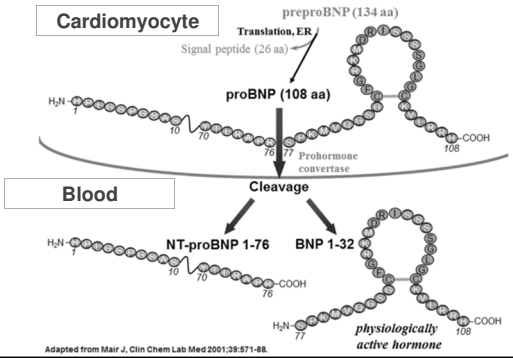


Packer et al. Circulation 2014

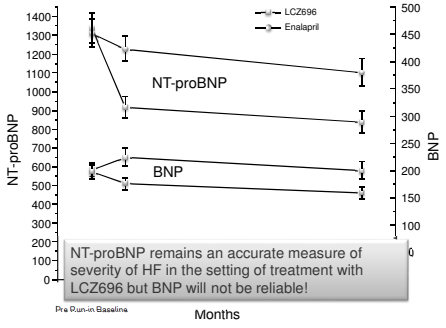
*Includes repeat episodes



NT pro BNP and BNP



Mechanism: NT-proBNP and BNP



McMurray et al. NEJM 2014

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

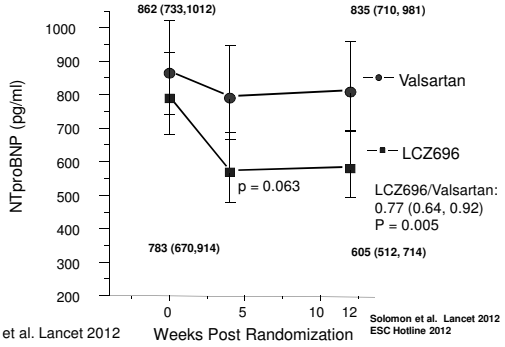
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

- The clinical strategy of inhibition of the renin-angiotensin system with **ACE inhibitors** (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

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

- The use of **ACE inhibitors** is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality (IA)
- 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 ACE inhibitors because of cough or angioedema (IA)
- In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, **replacement by an ARNI** is recommended to further reduce morbidity and mortality (IB-R)
  - ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (IIIB-R)

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



Solomon et al. Lancet 2012

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