ATRIUM CARDIOLOGY COLLABORATIVE

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ACE High? Reshuffling the Deck in the Management of Heart Failure

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Disclosure

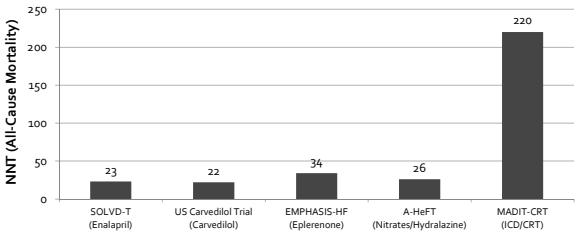
Nothing to disclose

Guideline-Directed Medical Therapy in Heart Failure with Reduced Ejection Fraction

- **ACEi or ARB + Beta Blocker** (Class I, LOE A)
  - *ICD ± CRT in eligible patients*
- Patients with volume overload and NYHA Class II-IV → Add **Loop Diuretic** (Class I, LOE C)
- African Americans who are persistently symptomatic → Add **Nitrates / Hydralazine** (Class I, LOE A)
- NYHA Class II-IV with CrCl > 30 mL/min and K < 5.0 mEq/L → Add **Aldosterone Antagonist** (Class I, LOE A)

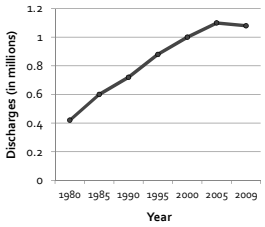
ACEi = Angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CrCL = creatinine clearance, CRT = cardiac resynchronization therapy, LOE = level of evidence, NYHA = New York Heart Association, ICD = implantable cardioverter defibrillator. Adapted from Yancy CW, et al. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.

Reductions in All-Cause Mortality Among Common Heart Failure Therapies

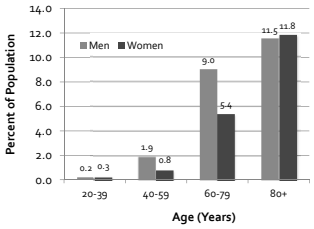


ICD = implantable cardioverter defibrillator, NNT = number needed to treat
Adapted from N Engl J Med. 2014 Sep 11;371(11):1062-4.

Discharges from Hospitalization Due to Heart Failure (1980-2009)



Prevalence of Heart Failure, by Sex and Age (2005-2008)



Adapted from JACC Heart Fail. 2013 Feb;1(1):1-20.

Natriuretic Peptide System

ProBNP → NT-proBNP, BNP

- NEP → Inactive fragments
- Vasoconstriction
- Sympathetic tone
- Aldosterone release
- Natriuretic/diuresis

Heart Failure

LCZ696 → Sacubitril, Valsartan

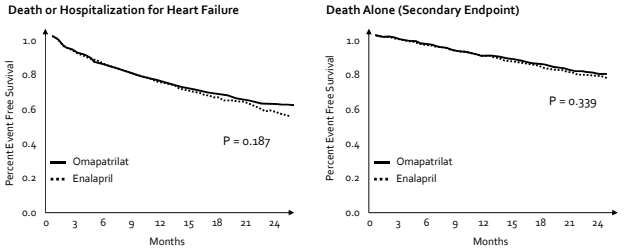
Renin-Angiotensin-Aldosterone System

Angiotensinogen → Angiotensin I → Angiotensin II → AT1 Receptor

- Vasoconstriction
- Sympathetic tone
- Aldosterone release
- Cardiac fibrosis
- Ventricular hypertrophy

AT = angiotensin, BPN = brain (or B-type) natriuretic peptide, NEP = neprilysin
Adapted from JACC Heart Fail. 2014 Dec;2(6):663-70.

OCTAVE: Omipatrilat versus Enalapril



Adapted from Circulation. 2002 Aug 20;106(8):920-6.

PARADIGM-HF

Inclusion Criteria

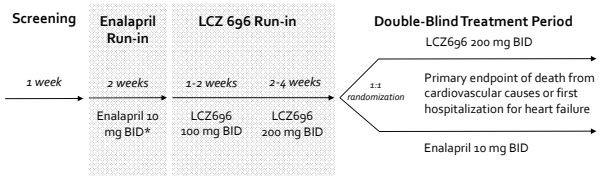
- Age ≥ 18 years
- NYHA functional class II-IV
- Ejection fraction ≤ 40%
- BNP ≥ 150 pg/mL or BNP ≥ 100 pg/mL and hospitalization for heart failure in prior 12 months*
- Stable dose of ACE inhibitor or ARB (equivalent to enalapril 10 mg/day) and beta blocker for ≥ 4 weeks

Select Exclusion Criteria

- Symptomatic hypotension
- Systolic blood pressure < 100 mmHg
- Estimated GFR < 30 mL/min/1.73 m²
- Serum K^+ > 5.2 mEq/L
- Prior intolerance to target doses of ACE inhibitors or ARBs
- Known history of angioedema

*Or NT-proBNP ≥ 600 pg/mL or NT-proBNP ≥ 400 pg/mL and heart failure hospitalization within prior 12 months
ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, BNP = brain natriuretic peptide, GFR glomerular filtration rate, NYHA = New York Heart Association. Eur J Heart Fail. 2013 Sep;15(9):1062-73.

PARADIGM-HF



*Patients could be started at 5 mg BID initially and then up-titrated to 10 mg BID after 1 week
Eur J Heart Fail. 2013 Sep;15(9):1062-73.

PARADIGM-HF

Reason for Discontinuation *10,514 patients entered run-in phase*	Enalapril Run-in *1102 discontinuations (10.5%)*	LCZ696 Run-in *977 discontinuations (9.3%)*
Adverse Event	591 (5.6%)	547 (5.8%)
Abnormal Laboratory/Test	66 (0.6%)	58 (0.6%)
Withdrew Consent	171 (1.6%)	100 (1.1%)
Protocol-Related Issue *Protocol deviation, administrative problem, or lost to follow-up*	138 (1.3%)	146 (1.6%)
Died	49 (0.5%)	47 (0.5%)
Other	87 (0.8%)	79 (0.8%)

N Engl J Med. 2014 Sep 11;371(11):993-1004.

PARADIGM-HF

Baseline Characteristic (Select)	Enalapril *(n=4212)*	LCZ696 *(n=4187)*
Age (years)	63.8 ± 11.3	63.8 ± 11.5
Female sex (%)	22.6%	21.0%
White, Black, Asian (%)	66.0%, 5.1%, 17.8%	66.0%, 5.1%, 18.1%
Systolic blood pressure (mmHg)	121 ± 15	122 ± 15
Serum creatinine (mg/dL)	1.12 ± 0.3	1.13 ± 0.3
NYHA functional class II, III (%)	69.3%, 24.9%	71.6%, 23.1%
Left ventricular ejection fraction (%)	29.4 ± 6.3	29.6 ± 6.1
B-type natriuretic peptide (pg/mL)	251 (153-465)	255 (155-474)
Prior hospitalization for heart failure (%)	63.3%	62.3%

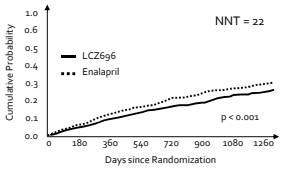
NYHA = New York Heart Association
Adapted from N Engl J Med. 2014 Sep 11;371(11):993-1004.

PARADIGM-HF

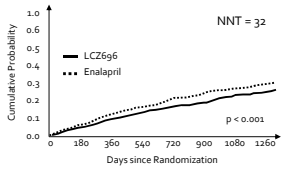
Baseline Medication Use	Enalapril *(n=4212)*	LCZ696 *(n=4187)*
Pretrial use of an ACE inhibitor (%)	77.5%	78.0%
Pretrial use of an ARB (%)	22.9%	22.2%
Beta-blocker (%)	92.9%	93.1%
Aldosterone antagonist (%)	57.0%	54.2%
Digoxin (%)	31.2%	29.2%
Diuretic (%)	80.1%	80.3%
Implantable cardioverter-defibrillator (%)	14.7%	14.9%
Cardiac resynchronization therapy (%)	6.7%	7.0%

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker
Adapted from N Engl J Med. 2014 Sep 11;371(11):993-1004.

Primary Composite Endpoint



Death from Cardiovascular Causes Alone



Outcome	Enalapril (n=4212)	LCZ696 (n=4187)	HR (95% CI)	p-value
Primary endpoint (death from cardiovascular causes or first hospitalization for worsening heart failure) (n, %)	1117 (26.5%)	914 (21.8%)	0.80 (0.73-0.87)	< 0.001
Death from cardiovascular causes (n, %)	693 (16.5%)	558 (13.3%)	0.80 (0.71-0.89)	< 0.001
First hospitalization for worsening heart failure (n, %)	658 (15.6%)	537 (12.8%)	0.79 (0.71-0.89)	< 0.001

HR = hazard ratio, CI = confidence interval.
Adapted from N Engl J Med. 2014 Sep 11;371(11):993-1004.

PARADIGM-HF

Secondary Endpoints	Enalapril (n=4212)	LCZ696 (n=4187)	HR (95% CI)	p-value
Death from any cause	835 (19.8%)	711 (17.0%)	0.84 (0.76-0.93)	< 0.001
Change in KCCQ score	-4.63 ± 0.36	-2.99 ± 0.36	1.64 (0.63-2.65)	< 0.001
New-onset atrial fibrillation	83 (3.1)	84 (3.1)	0.97 (0.72-1.31)	0.83
Decline in renal function*	108 (2.5)	94 (2.2)	0.86 (0.65-1.13)	0.23

*Defined as end-stage renal disease or ≥ 50% decrease in GFR or a decrease in GFR of ≥ 30 mL/min/1.73 m² to less than 60 mL/min/1.73 m²

GFR = glomerular filtration rate, KCCQ = Kansas City Cardiomyopathy Questionnaire
Adapted from N Engl J Med. 2014 Sep 11;371(11):993-1004.

PARADIGM-HF

Safety Endpoints (n, %)	Enalapril (n=4212)	LCZ696 (n=4187)	p-value
Symptomatic hypotension	388 (9.2)	588 (14.0)	< 0.001
Symptomatic hypotension with systolic BP < 90 mmHg	59 (1.4)	112 (2.7)	< 0.001
Serum creatinine ≥ 2.5 mg/dL	188 (4.5)	139 (3.3)	0.007
Serum creatinine ≥ 3.0 mg/dL	83 (2.0)	63 (1.5)	0.10
Serum potassium > 5.5 mEq/L	727 (17.3)	674 (16.1)	0.15
Serum potassium > 6.0 mEq/L	236 (5.6)	181 (4.3)	0.007
Cough	601 (14.3)	474 (11.3)	< 0.001
Angioedema	10 (0.2)	19 (0.4)	NS

Fewer overall discontinuations of LCZ696 compared to enalapril (17.8% vs. 19.8%, respectively, p=0.02) and fewer due to adverse effects (10.7% vs. 12.3%, respectively, p=0.03)

BP = blood pressure, NS = non-significant
Adapted from N Engl J Med. 2014 Sep 11;371(11):993-1004.

Follow-Up Analyses of PARADIGM-HF

- Progression analysis showed a 23% reduction in heart failure hospitalizations with LCZ696 (851 vs. 1079, p<0.001)[1]
- Mode of death analysis showed reductions with LCZ696 driven by sudden cardiac death (6.0% vs. 7.4%, p=0.008)[2]
- Age analysis showed consistent benefit of LCZ 696 across subgroups of < 55, 55-65, 65-74, and ≥ 75 years of age[3]

[1]Circulation. 2015 Jan 6;131(1):54-61. [2]Eur Heart J. 2015 Aug 7;36(30):1990-7. [3]Eur Heart J. 2015 Oct 7;36(38):2576-84.

Cost Effectiveness and Value

- Average wholesale price approximately $5,400[1]
- Cost-effectiveness estimated at $50,915 per QALY gained if benefits persist for over 5 years[2]
- Cost-effectiveness exceeds $100,000 per QALY gained if duration of benefit is 3.3 years or less[2]
- To not exceed the growth of health care costs (in proportion with US economic growth), would need to be $4168 or less[2]

[1]Sacubitril and valsartan monograph. Lexicomp Online® , Lexi-Drugs® , Hudson, Ohio: Lexi-Comp, Inc.; 21 February 2016. [2]JAMA Intern Med. 2016 Feb 1;176(2):249-50.

Remaining Controversies

- Suboptimal background therapy
- Efficacy and safety in specific subpopulations
  - Black patients
  - NYHA Class I, IV, and ADHF
- Patients not previously on ACE inhibitors or ARBs
- Impact on blood pressure
- ProBNP and NT-proBNP monitoring
- Off-target effects of neprilysin inhibition

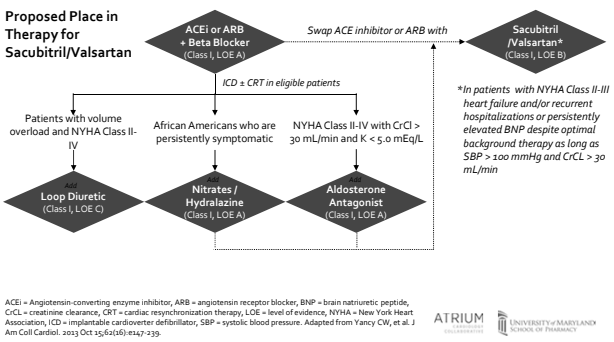
ACE = angiotensin-converting enzyme, ADHF = acute decompensated heart failure, ARB = angiotensin receptor blocker, BNP = brain or B-type natriuretic peptide, NYHA = New York Heart Association

Accumulated Trial Experience

ACE Inhibitors	Angiotensin Receptor Blockers	Neprilysin / Angiotensin Receptor Blockers
• ATLAS • CHARM Added • CONSENSUS I, II* • ELITE I, II • OPTIMAAL* • SOLVD • SAVE* • TRACE* • V-HeFT II • VALIANT*	• CHARM Overall • CHARM Added • CHARM Preserved • CHARM Alternative • ELITE I, II • HEAAL • OPTIMAAL* • VAL-HeFT • VALIANT*	• PARADIGM-HF

**Denotes trials of left ventricular dysfunction after myocardial infarction*

ACE = Angiotensin-converting enzyme



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Sacubitril/Valsartan

Approved Indications

- To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic NYHA Class II-IV heart failure with reduced ejection fraction
- Administered in conjunction with other heart failure therapies in place of an ACE inhibitor or ARB

Contraindications

- Patients with hypersensitivity to sacubitril or valsartan
- In patients with a history of angioedema related to previous ACE inhibitor or ARB therapy
- Concomitant ACE inhibitor use; must allow for 36-hour washout
- Concomitant aliskiren in patients with diabetes

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, NYHA = New York Heart Association. From Entresto™ Package Insert. Novartis Pharmaceuticals Corporation. East Hanover, NJ. 2015 August.

Sacubitril/Valsartan

Population	Initial Dose
ACE inhibitor equivalent to enalapril > 10 mg/day, *or* ARB equivalent to valsartan > 160 mg/day	49/51 mg twice daily
Naïve to ACE inhibitor or ARB, *or* ACE inhibitor equivalent to enalapril ≤ 10 mg, *or* ARB equivalent to valsartan ≤ 160 mg/day	24/26 mg twice daily
Severe renal impairment (GFR < 30 mL/min/1.73 m²)	24/26 my twice daily
Moderate hepatic impairment (Child-Pugh B)	24/26 mg twice daily

Titration Schedule: Double the dose of sacubitril/valsartan every 2-4 weeks as tolerated to a target dose of 97/103 mg twice daily

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, GFR = glomerular filtration rate. From Entresto™ Package Insert. Novartis Pharmaceuticals Corporation. East Hanover, NJ. 2015 August.

Sacubitril/Valsartan

Precautions/Warnings

- Pregnancy (boxed warning)
- Breastfeeding not recommended
- Angioedema
- Hypotension
- Impaired renal function
- Hyperkalemia

Drug-Drug Interactions

- Other RAAS inhibitors
- Potassium-sparing diuretics
- NSAIDs
- Lithium
- Inhibits OATP1B1 and OATP1B3 transporters but effects unknown
- Minimal CYP450 involvement

CYP = cytochrome P, NSAIDs = non-steroidal anti-inflammatory drugs, OATP = organic anion transporter protein, RAAS = renin-angiotensin-aldosterone system. From Entresto™ Package Insert. Novartis Pharmaceuticals Corporation. East Hanover, NJ. 2015 August.

Other Updates in Heart Failure

- Approval of ivabradine to prevent hospitalization in patients with heart failure with reduced ejection fraction and normal sinus rhythm with heart rate ≥ 70 beats per minute on maximally-tolerated dose of beta blocker
- Long-acting nitrates shown not to be beneficial in heart failure with preserved ejection fraction