Continued Evolution of Heart Failure Guideline-Directed Medical Therapy (GDMT)

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Disclosure

Nothing to disclose.

Objectives: Live Program

- To describe recent changes to the ACC/AHA Heart Failure Guidelines.
- To understand the role of I_f channel inhibitors in the management of HF.
- To recognize the role of neprilysin inhibition in the management of HF.

Epidemiology

- Over 5 million Americans diagnosed with HF
- Over 800,000 new cases diagnosed annually
- Over 1 million hospitalizations annually
  - Approximately 25% readmission rate within 1 month
- Total annual cost of HF is > $30 billion
- Mortality rate remains 50% at 5 years

Circulation 2014; 129:e28-e292

Classification of Recommendations and Levels of Evidence

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care

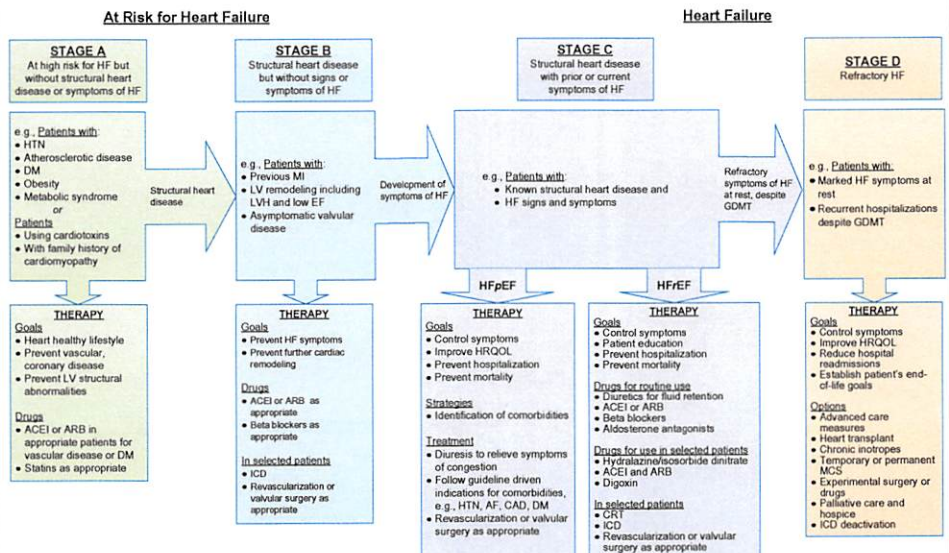
A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/ efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

JACC 2013; 128: e240-327

Stages, Phenotypes and Treatment of HF



JACC 2013; 128: e240-327

Definition of Heart Failure

Classification	Ejection Fraction	Description
I. Heart Failure with Reduced Ejection Fraction (HF*r*EF)	≤40%	Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HF*r*EF and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart Failure with Preserved Ejection Fraction (HF*p*EF)	≥50%	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, Borderline	41% to 49%	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HF*p*EF.
b. HF*p*EF, Improved	>40%	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

JACC 2013; 128: e240-327

Classification of Heart Failure

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF.	None	
B	Structural heart disease but without signs or symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions.		

JACC 2013; 128: e240-327

Risk Scoring

Validated multivariable risk scores can be useful to estimate subsequent risk of mortality in ambulatory or hospitalized patients with HF.

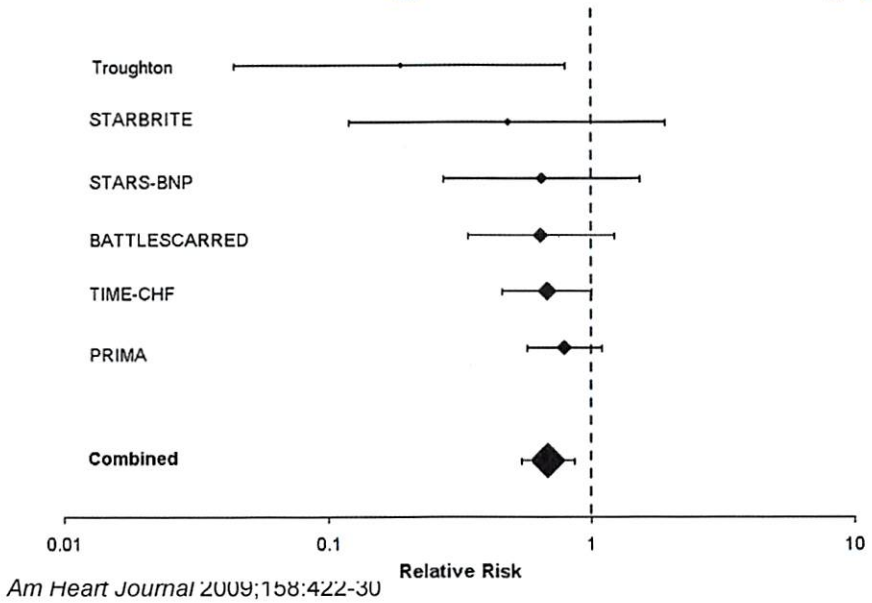
JACC 2013; 128: e240-327

Risk Scores to Predict Outcomes in HF

Risk Score	Reference (from full-text guideline)/Link
Chronic HF	
All patients with chronic HF	
Seattle Heart Failure Model	(204) / http://SeattleHeartFailureModel.org
Heart Failure Survival Score	(200) / http://handheld.softpedia.com/get/Health/Calculator/HFSS-Calc-37354.shtml
CHARM Risk Score	(207)
CORONA Risk Score	(208)
Specific to chronic HFpEF	
I-PRESERVE Score	(202)
Acutely Decompensated HF	
ADHERE Classification and Regression Tree (CART) Model	(201)
American Heart Association Get With the Guidelines Score	(206) /http://www.heart.org/HEARTORG/HealthcareProfessional/GetWithTheGuidelinesHFStroke/GetWithTheGuidelinesHeartFailureHomePage/Get-With-The-Guidelines-Heart-Failure-Home-%20Page_UCM_306087_SubHomePage.jsp
EFFECT Risk Score	(203) / http://www.ccort.ca/Research/CHFRiskModel.aspx
ESCAPE Risk Model & Discharge Score	(215)
OPTIMIZE HF Risk-Prediction Nomogram	(216)

JACC 2013; 128: e240-327

BNP Monitoring: "Guided Therapy"



Am Heart Journal 2009;158:422-30

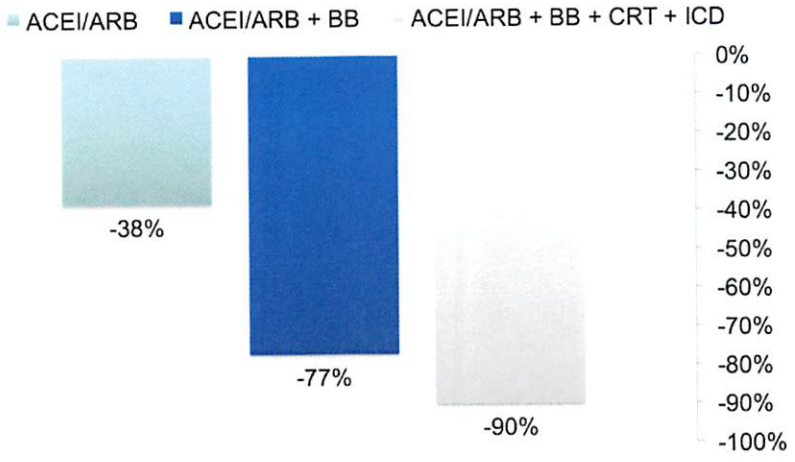
Recommendations for BNP Monitoring in HF

Biomarker, Application	Setting	COR	LOE
Natriuretic peptides			
Diagnosis or exclusion of HF	Ambulatory, Acute	I	A
Prognosis of HF	Ambulatory, Acute	I	A
Achieve GDMT	Ambulatory	IIa	B
Guidance of acutely decompensated HF therapy	Acute	IIb	C

JACC 2013; 128: e240-327

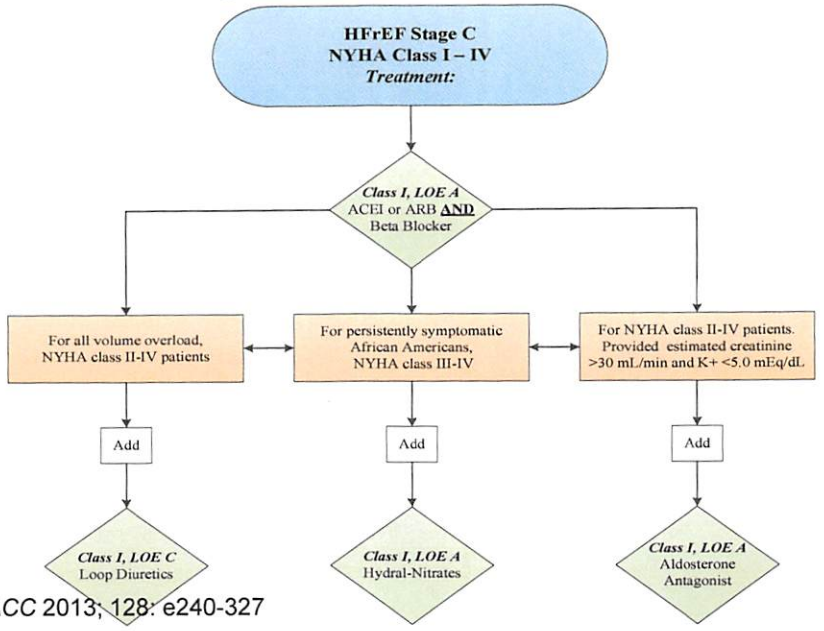
Incremental Benefit with HF Therapies

(Cumulative % Reduction in Odds of Death at 24 Months)



J Am Heart Assoc 2012;1:16-26

Pharmacologic Treatment for Stage C HF*r*EF



JACC 2013; 128: e240-327

Stage C HF*r*EF

Aldosterone receptor antagonists (ARAs) are recommended in patients with NYHA class II-IV and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for ARAs.

Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HF*r*EF.

Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine greater than 2.5 mg/dL in men or greater than 2.0 mg/dL in women (or estimated glomerular filtration rate <30 mL/min/1.73m^2), and/or potassium above 5.0 mEq/L.

JACC 2013; 128: e240-327

Medical Therapy for Stage C HF*r*EF: Magnitude of Benefit Demonstrated in RCTs

GDMT	RR Reduction in Mortality	NNT for Mortality Reduction (Standardized to 36 months)	RR Reduction in HF Hospitalizations
ACE inhibitor or ARB	17%	26	31%
Beta blocker	34%	9	41%
Aldosterone antagonist	30%	6	35%
Hydralazine/nitrate	43%	7	33%

JACC 2013; 128: e240-327

Drugs Commonly Used for HF*r*EF (Stage C HF)

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials
ACE Inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	122.7 mg/d (421)
Enalapril	2.5 mg twice	10 to 20 mg twice	16.6 mg/d (412)
Fosinopril	5 to 10 mg once	40 mg once	---
Lisinopril	2.5 to 5 mg once	20 to 40 mg once	32.5 to 35.0 mg/d (444)
Perindopril	2 mg once	8 to 16 mg once	---
Quinapril	5 mg twice	20 mg twice	---
Ramipril	1.25 to 2.5 mg once	10 mg once	---
Trandolapril	1 mg once	4 mg once	---
ARBs			
Candesartan	4 to 8 mg once	32 mg once	24 mg/d (419)
Losartan	25 to 50 mg once	50 to 150 mg once	129 mg/d (420)
Valsartan	20 to 40 mg twice	160 mg twice	254 mg/d (109)
Aldosterone Antagonists			
Spironolactone	12.5 to 25 mg once	25 mg once or twice	26 mg/d (424)
Eplerenone	25 mg once	50 mg once	42.6 mg/d (445)

JACC 2013; 128: e240-327

Drugs Commonly Used for HF*r*EF (Stage C HF)

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials
Beta Blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d (118)
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d (446)
Carvedilol CR	10 mg once	80 mg once	---
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once	159 mg/d (447)
Hydralazine & Isosorbide Dinitrate			
Fixed dose combination (423)	37.5 mg hydralazine/ 20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/ 40 mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate (448)	Hydralazine: 25 to 50 mg, 3 or 4 times daily and isorsorbide dinitrate: 20 to 30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses	---

JACC 2013; 128: e240-327

Stage C HF*r*EF

No Benefit

Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use.

Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II-IV symptoms and HF*r*EF or HF*p*EF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.

JACC 2013; 128: e240-327

Treatment of HF*p*EF

Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B
Diuretics should be used for relief of symptoms due to volume overload	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF	IIa	C
ARBs might be considered to decrease hospitalizations in HFpEF	IIb	B
Nutritional supplementation is not recommended in HFpEF	III: No Benefit	C

JACC 2013; 128: e240-327

Transitions of Care

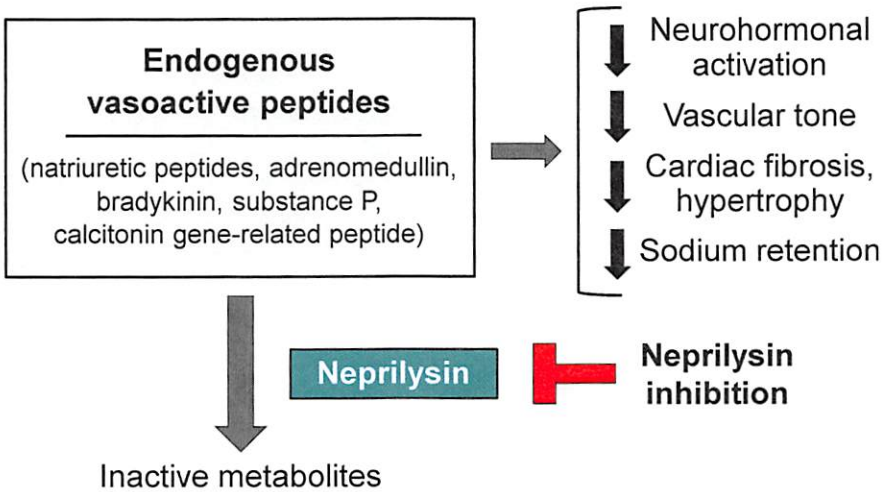
Multidisciplinary HF disease-management programs are recommended for patients at high risk for hospital readmission, to facilitate the implementation of GDMT, to address different barriers to behavioral change, and to reduce the risk of subsequent rehospitalization for HF.

Scheduling an early follow-up visit (within 7 to 14 days) and early telephone follow-up (within 3 days) of hospital discharge is reasonable.

Use of clinical risk prediction tools and/or biomarkers to identify patients at higher risk for postdischarge clinical events is reasonable.

JACC 2013; 128: e240-327

Neprilysin Inhibition



Sacubitril/Valsartan (Entresto™)

Increased endogenous compensatory peptides

- ↑ Vasodilation
- ↑ Natriuretic/diuretic effects
- ↓ Proliferation
- ↓ Ventricular hypertrophy
- ↓ Sympathetic tone
- ↓ Aldosterone secretion
- ↓ Vascular remodeling

Suppressed RAAS-mediated effects

- ↓ Vasoconstriction
- ↓ Sodium/water retention
- ↓ Ventricular hypertrophy
- ↓ Aldosterone secretion
- ↓ Cardiac fibrosis
- ↓ Sympathetic tone
- ↓ Systemic vascular resistance

PARADIGM-HF: Entry Criteria

Inclusion Criteria

- Age ≥18 yrs
- NYHA Class II-IV
- LVEF ≤40%-> amended to 35%
- BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL
- If hospitalized for HF in past 12 months, BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL
- Stable dose for 4 weeks on beta-blocker and ACEI/ARB equivalent to at least enalapril 10 mg daily

Exclusion Criteria

- Symptomatic hypotension
- SBP <100 mmHg (screening) or <95 mmHg (randomization)
- eGFR <30 mL/min/1.73 m^2
- ↓ eGFR >25%
- Serum K+ >5.2 (screening or >5.4 (randomization)
- Hx of angioedema
- Unacceptable side effects with ACEI/ARB

N Engl J Med 2014; 371:933-1004

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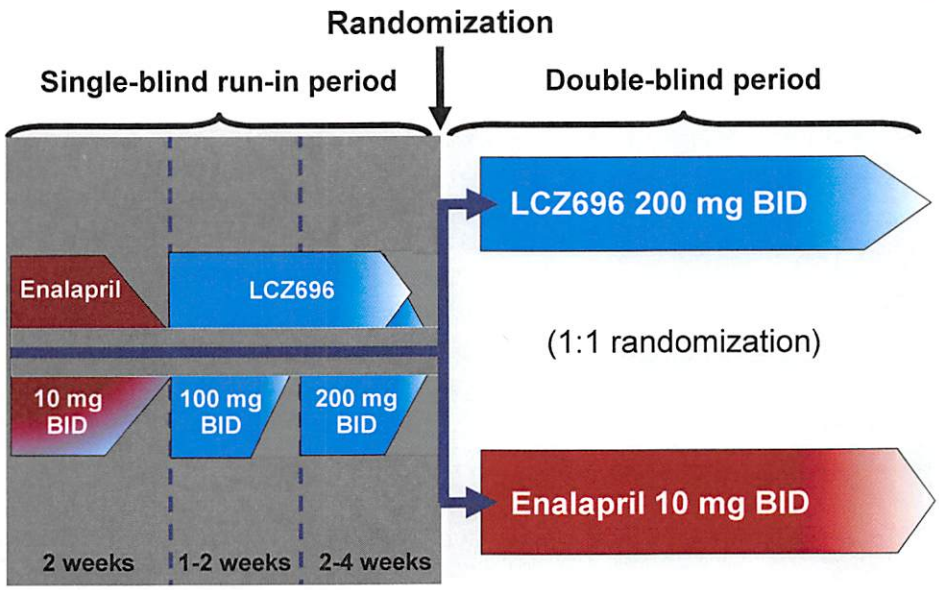
PARADIGM-HF: Study Design



PARADIGM-HF: Baseline Characteristics

	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
White/Black/Asian	66% / 5.1% / 18.1%	66% / 5.1% / 17.8%
Clinical Features of Heart Failure		
Ischemic cardiomyopathy (%)	59.9%	60.1%
LVEF (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Hospitalization for HF (%)	62.3%	63.3%
BNP (pg/ml)	255 (155-474)	251 (153-465)
NT-pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
Medical History		
Hypertension (%)	70.9%	70.5%
Myocardial infarction (%)	43.4%	43.1%
Diabetes (%)	35%	35%
Atrial fibrillation (%)	36.2%	37.4%

PARADIGM-HF: Baseline Characteristics

	LCZ696 (n=4187)	Enalapril (n=4212)
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
Serum Creatinine (mg/dL)	1.13 ± 0.3	1.12 ± 0.3
Treatment at Randomization		
Diuretic	80.3%	80.1%
Beta-blocker	93.1%	92.9%
Aldosterone antagonist	54.2%	57.0%
Digoxin	29.2%	31.2%
Implantable defibrillator	14.9%	14.7%
Cardiac resynchronization therapy	7%	6.7%

PARADIGM-HF: Endpoints

	Entresto (n=4,187) n (%)	Enalapril (n=4,212) n (%)	HR (95% CI)	p-value
Primary Outcome				
Cardiovascular death or heart failure hospitalization	914 (21.8)	1,117 (26.5)	0.80 (0.73, 0.87)	< 0.001
Cardiovascular death	558 (13.3)	693 (16.5)	0.80 (0.71, 0.89)	< 0.001
Heart failure hospitalization	537 (12.8)	658 (15.6)	0.79 (0.71, 0.89)	< 0.001
Secondary Outcomes				
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (0.76, 0.93)	< 0.001
Change in KCCQ at 8 months	-2.99 ± 0.36	-4.63 ± 0.36	1.64 (0.63-2.65)	0.001
New-onset atrial fibrillation	84 (3.1)	83 (3.1)	0.97 (0.72-1.31)	0.83
Decline in renal function	94 (2.2)	108 (2.6)	0.86 (0.65-1.13)	0.28

Median Follow-up: 27 months
Mean Dose: Enalapril 18.9 +/- 3.4 mg, LCZ696 375 +/- 71 mg

PARADIGM-HF: Adverse Events

	Ernesto (n=4187)	Enalapril (n=4212)	p-value
Prospectively identified adverse events			
Symptomatic hypotension	588 (14%)	388 (9.2%)	< 0.001
Serum potassium > 6.0 mmol/l	181 (4.3%)	236 (5.6%)	0.007
Serum creatinine ≥ 2.5 mg/dl	139 (3.3%)	188 (4.5%)	0.007
Cough	474 (11.3	601	< 0.001
Discontinuation for adverse event			
Discontinuation for any event	449 (10.7%)	516 (12.3%)	0.03
Discontinuation for hypotension	36 (0.9%)	29 (0.7%)	0.38
Discontinuation for hyperkalemia	11 (0.3%)	15 (0.4%)	0.56
Discontinuation for renal impairment	29 (0.7%)	59 (1.4%)	0.002
Angioedema (adjudicated)			
No treatment or antihistamines only	10 (0.2%)	5 (0.1%)	0.19
Catecholamines or glucocorticoids	6 (0.1%)	4 (0.1%)	0.52
Hospitalized; no airway compromise	3 (0.1%)	1 (<0.1%)	0.31
Airway compromise	0	0	----

Entresto™ Dosing

Criteria	Initial Entresto Dose
Enalapril > 10 mg/d or equivalent* Valsartan > 160 mg/d or equivalent	49/51 mg twice daily
Enalapril ≤ 10 mg/d or equivalent* Valstartan ≤ 160 mg/day or equivalent No ACEI or ARB	24/26 mg twice daily
Severe renal dysfunction (eGFR < 30 mL/min/1.73m^2) Moderate hepatic dysfunction (Child-Pugh Class B)	24/26 mg twice daily
Severe hepatic dysfunction (Child-Pugh Class C)	Use not recommended

*Washout period of 36 hours required if switching from ACEI

- Double dose every 2 to 4 weeks, as tolerated
- Target dose 97/103 mg twice daily

Entresto™ Package Insert 2015

Entresto™ Indications/Contraindications

- Indication
  - To reduce the risk of CV death and HF hospitalization in patients with chronic HF (NYHA Class II-IV) and reduced EF
  - Administered in conjunction with other HF therapies, in place of an ACE inhibitor or ARB
- Contraindications
  - Concomitant ACE inhibitor
    - Angioedema risk
    - Washout period needed, 36 hours
  - History of angioedema to prior ACE inhibitor or ARB
  - Concomitant aliskiren in patients with diabetes

Entresto™ Package Insert 2015

Entresto™ Warnings/Precautious

- Boxed Warning
  - Pregnancy secondary RAAS inhibition
- Angioedema
  - Higher rate in Black than non-Black patients
- Hypotension
  - Correct volume or sodium depletion prior to initiation
- Renal dysfunction
  - Monitor renal function if renal artery stenosis
- Hyperkalemia
  - Less frequent that ACEI alone

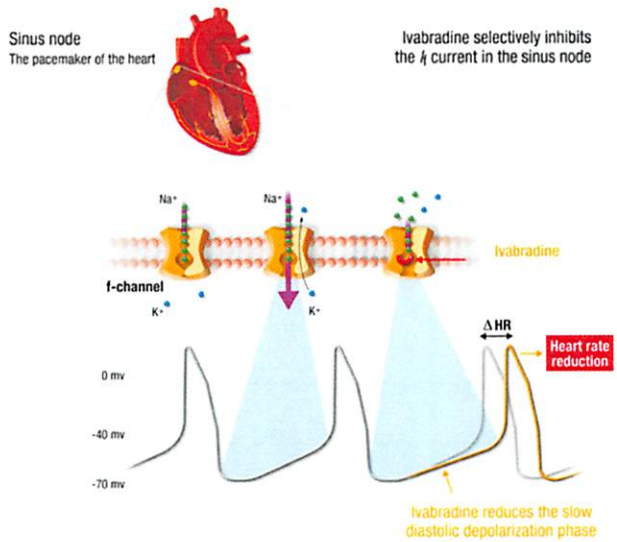
Entresto™ Package Insert 2015

Entresto™ Drug Interactions

- ACEI/ARB
- Aliskiren
  - Contraindicated if diabetes
  - Avoid use if eGFR < 60 mL/min/1.73 m^2
- Potassium-sparing diuretics
- NSAIDs/COX-2 inhibitors
- Lithium – increased concentrations

Entresto™ Package Insert 2015

Ivabradine (Corolan®)



Nature Reviews 2011; 10:903-14, *Drugs* 2004; 64-1757-65

SHIFT Trial:
Study Design/Entry Criteria

n = 6,558
Stable HF (NYHA II-IV), LVEF ≤ 35%, NSR w/ rHR ≥ 70 bpm,
Stable SOC therapy including max tolerated beta-blocker,
and hospitalization for worsening HF within prior 12 months

Ivabradine 5 mg BID* | Placebo

Primary endpoint: CV death or hospitalization for worsening HF

Median follow-up duration: 22.9 months

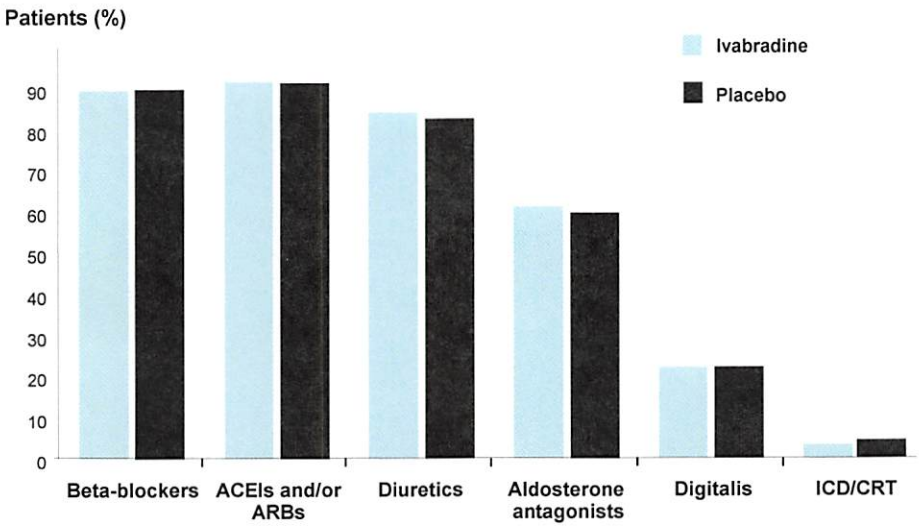
*Titrated at 2 weeks based upon HR and tolerability, target HR 50-60 bpm

The Lancet 2010; 376:875-885

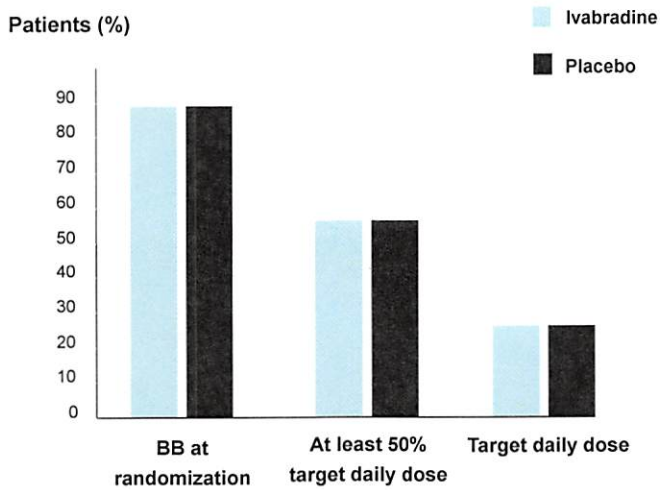
SHIFT Trial: Baseline Characteristics

	Ivabradine (n=3,241)	Placebo (n=3,264)
Age (mean yrs, SD)	61 (11)	60 (12)
Male (%)	76	77
NYHA II/III (%)	49/50	49/50
LVEF (mean %, SD)	29 (5)	29 (5)
Ischemic etiology	68%	67%
Hypertension	67%	66%
Diabetes	30%	31%
History of atrial fibrillation/flutter	8%	8%
Systolic BP (mean mmHg, SD)	122 (16)	121 (16)
HR (mean bpm, SD)	80 (10)	80 (10)
eGFR (mean mL/min/1.73 m^2, SD)	75 (23)	75 (23)

SHIFT Trial: Baseline Characteristics



SHIFT Trial: Baseline Characteristics

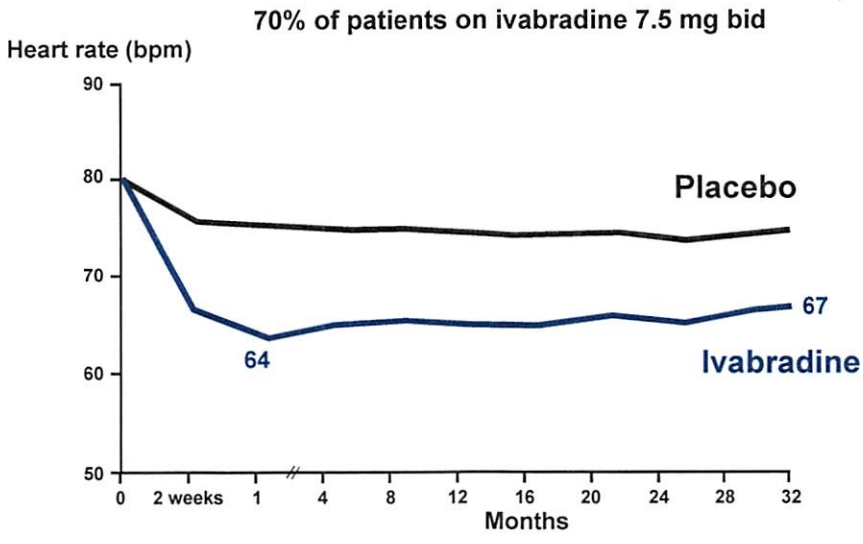


SHIFT Trial: Baseline Characteristics

Main reasons for not achieving beta-blocker target dose, %		
	Ivabradine n=2099	Placebo n=2126
Hypotension	44	45
Fatigue	32	32
Dyspnea	14	14
Dizziness	13	12
Bradycardia	6	6

Main reasons for not prescribing beta-blocker, %		
	Ivabradine n=344	Placebo n=341
COPD	37	32
Hypotension	17	20
Asthma	10	11
CV decompensation	7	9
Dizziness/bradycardia	7	5
Fatigue	5	6

Mean Heart Rate Reduction



SHIFT Trial: Primary Endpoint

Outcomes	Ivabradine (n=3241)	Placebo (n=3264)	HR (95% CI)	p value
CV death or HF hospitalization	793 (24%)	937 (29%)	0.82 (0.75–0.90)	<0.0001
CV death	449 (14%)	491 (15%)	0.91 (0.80-1.03)	0.128
HF hospitalization	16%	21%	0.74 (0.66–0.83)	<0.0001
All-cause death	503 (16%)	552 (17%)	0.90 (0.80-1.02)	0.092
All-cause hospitalization	1231 (38%)	1356 (42%)	0.89 (0.82–0.96)	0.003

SHIFT Trial:
Impact of HR on Outcomes

Baseline HR quintiles, bpm	HR (95% CI)	p value
70 to <72	1.00	--
72 to <75	1.15 (0.88–1.48)	0.308
75 to <80	1.33 (1.03–1.70)	0.027
80 to <87	1.80 (1.40–2.31)	<0.0001
≥87	2.34 (1.84–2.98)	<0.0001

SHIFT Trial: Select Adverse Events

	Ivabradine N=3232, n (%)	Placebo N=3260, n (%)	*p* value
All serious adverse events	**1450** (45%)	**1553** (48%)	**0.025**
All adverse events	2439 (75%)	2423 (74%)	0.303
Heart failure	804 (25%)	937 (29%)	0.0005
Symptomatic bradycardia	150 (5%)	32 (1%)	<0.0001
Asymptomatic bradycardia	184 (6%)	48 (1%)	<0.0001
Atrial fibrillation	306 (9%)	251 (8%)	0.012
Nervous system disorders	130 (4%)	178 (5%)	0.007
Blurred vision	17 (1%)	7 (<1%)	0.042
Phosphenes*	89 (3%)	17 (1%)	<0.0001

Adverse event leading to drug withdrawal:

- Symptomatic bradycardia 20 (1%) vs 5 (<1%), p=0.002
- Asymptomatic bradycardia 28 (1%) vs 5 (<1%), p<0.0001

*Transient enhanced brightness in a restricted area of the visual field

Corolan® Indications

- To reduce the risk of hospitalization for worsening HF in patients who meet the following:
  - Stable, symptomatic chronic HF with LVEF $\leq$ 35%
  - Sinus rhythm with resting HR $\geq$ 70 bpm
  - On maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use

Corolan® Package Insert 2015

Corolan® Contraindications

- Acute decompensated heart failure
- Blood pressure < 90/50 mmHg
- Sick sinus syndrome, sinoatrial block, or 3rd degree block, unless a functioning pacemaker is present
- Resting HR < 60 bpm prior to treatment
- Severe hepatic impairment
- Pacemaker dependence
- Strong CYP3A4 inhibitors*

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Corolan® Dosing

- Starting dose: 5 mg twice daily with meals
  - At 2 weeks, adjust dose to achieve a resting HF between 50-60 bpm
  - Thereafter, adjust dose as needed based on resting HR and tolerability
  - Max dose 7.5 mg twice daily
  - If history of conduction defects, or other patients in whom bradycardia could lead to hemodynamic compromise, initiate at 2.5 mg twice daily

Corolan® Package Insert 2015

Corolan® Drug Interactions

- Contraindicated with strong CYP3A4 inhibitors
  - Azole antifungals, macrolide antibiotics, nefazodone
- Avoid concomitant use with moderate CYP3A4 inhibitors
  - Diltiazem, verapamil, grapefruit juice
- Avoid concomitant use with CYP3A4 inducers
  - St. John's Wort, Rifampicin, barbiturates, phenytoin
- Negative chronotropes
  - Risk of bradycardia increases with other drugs that slow HR (e.g., digoxin, amiodarone, beta-blockers)
- Pacemakers
  - Not recommended if demand PMs set at 60 bpm

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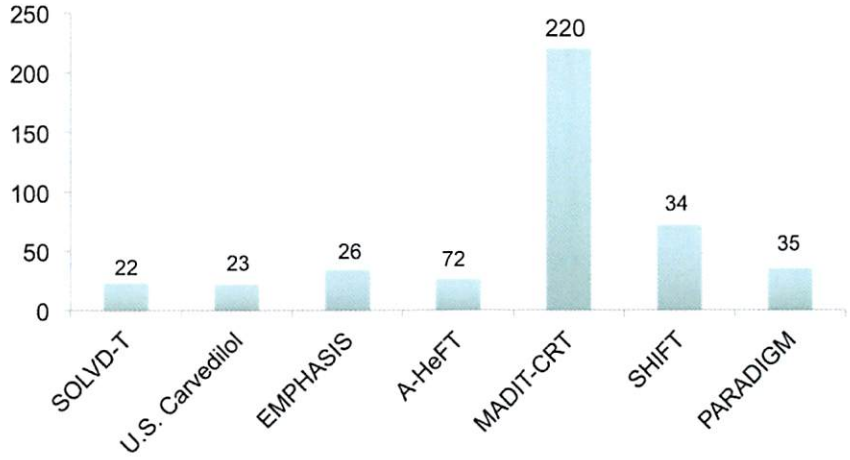
Comparison to Other Trials

Trial	Age (yr)	LVEF (%)	NYHAc (%)	HR (bpm)	SBP (mmHg)	ACEI/ARB (%)	Beta-blocker (%)	ARA (%)	ICD ± CRT (%)
Emphasis	68	26	100 II	72	124	93	86	NA	20
A-HeFT	57	24	95% III	N/A	126	87	74	38	18
MADIT-CRT	65	24	85% II	N/A	122	97	93	31	100
SHIFT	60	29	49 II, 50 III	79	121	91	89	60	5
Paradigm	64	<35 (88%)	70 II, 24 III	72	121	100	93	56	15

N Engl J Med 2014; 371: 1062-64

Number Needed to Treat:
All-cause Mortality



N Engl J Med 2014; 371: 1062-64

Conclusions

- Evidence-based guideline directed diagnosis, evaluation and therapy should be the mainstay for all patients with HF.
- Effective implementation of guideline-directed best quality care reduces mortality, improves QOL and preserves health care resources.
- Several potential new and emerging therapies may further advance management of the HF population. Ongoing research is needed to answer remaining questions including optimal management of HF*p*EF and ADHF.