

Heart Failure - Medical Management

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Objectives

- Discuss pharmacological management of heart failure
- Recognize new heart failure therapies including sacubitril-valsartan and ivabradine and understand their role in treating heart failure
- Review the signs of advanced heart failure and understand when to refer to a heart failure specialist

Heart Failure Statistics

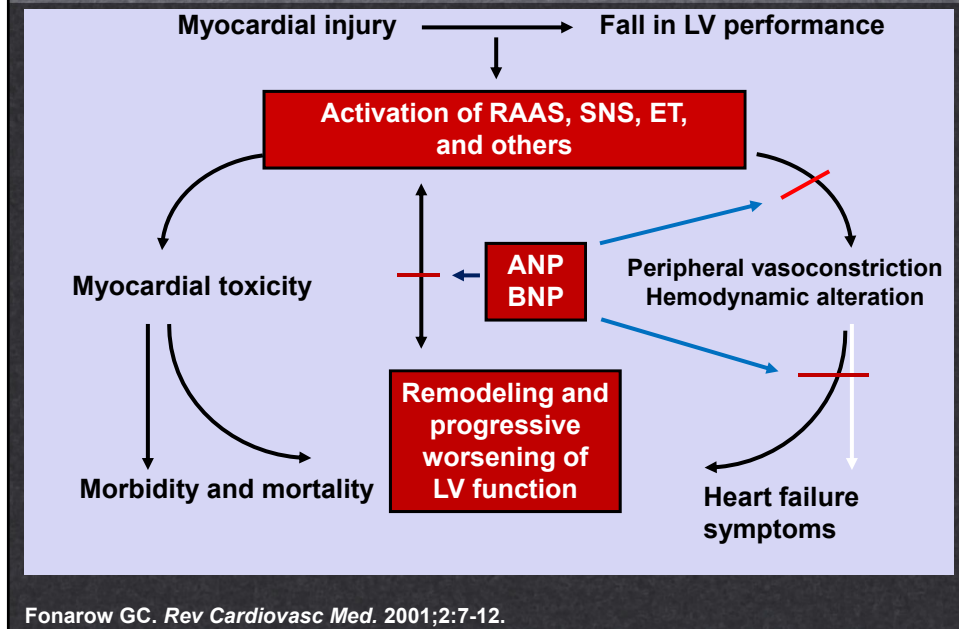
- Incidence is 10 per 1000 cases > age 65
- At age 40, lifetime risk is 1 in 5
- Mortality rate in large population studies remains 50% at 5 years.
- Over 1.1 million HF hospitalizations per year.
- With each HF hospitalization, survival goes down

Benjamin, et al. Circulation 2017.
AHA Statistics 2011

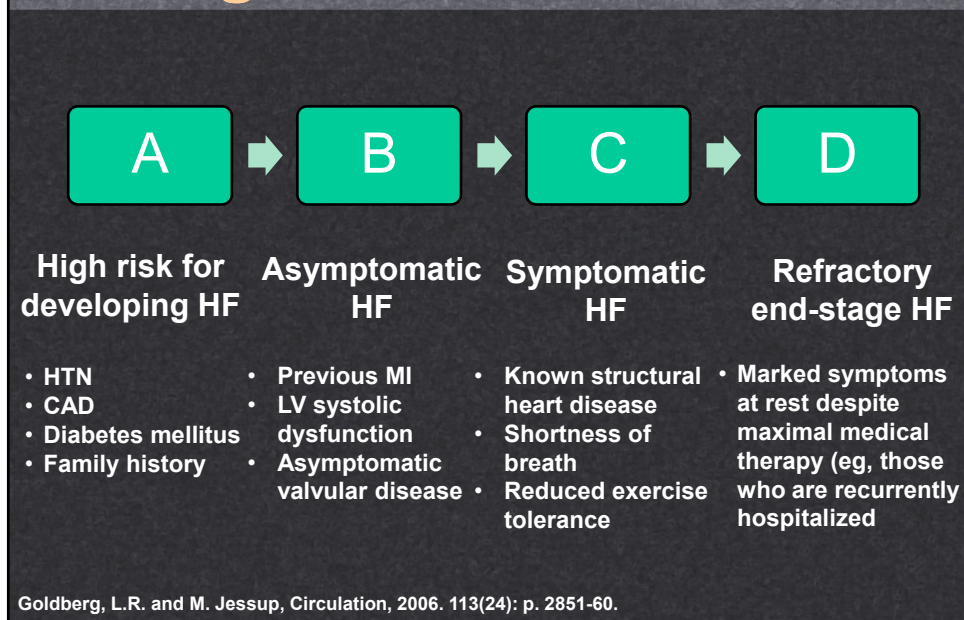
Heart Failure Definitions

- HFrEF (“systolic HF”): LVEF \leq 40%
- HFpEF (“diastolic HF”): LVEF \geq 40%

Heart Failure Pathophysiology



Stages of Heart Failure



2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary

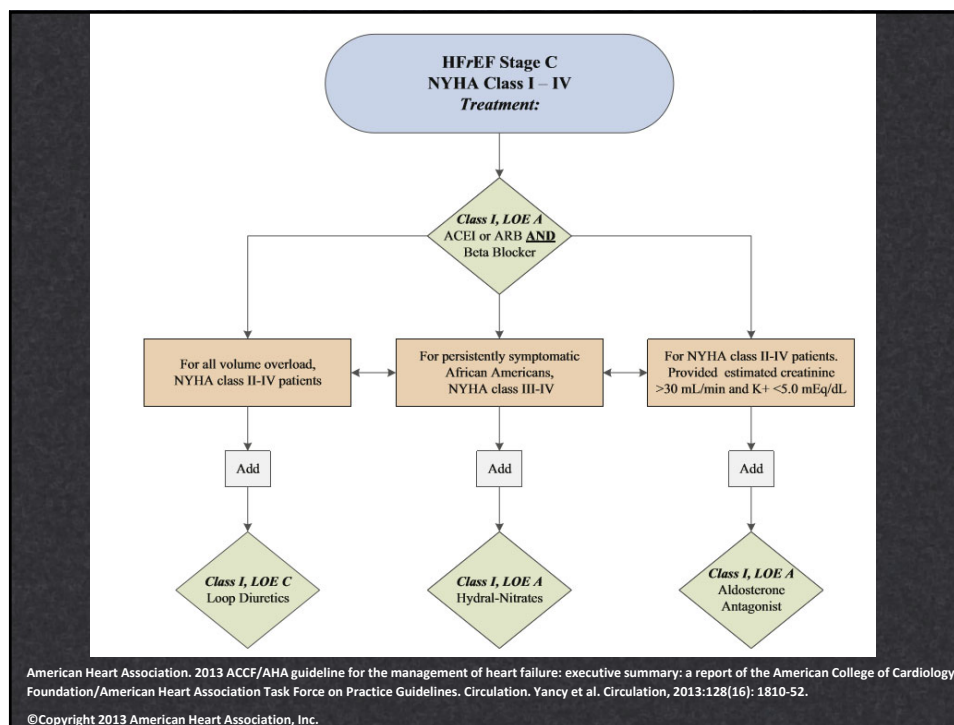
A Report of the American College of Cardiology Foundation/
American Heart Association Task Force on Practice Guidelines

*Developed in Collaboration With the American College of Chest Physicians, Heart Rhythm Society,
and International Society for Heart and Lung Transplantation*

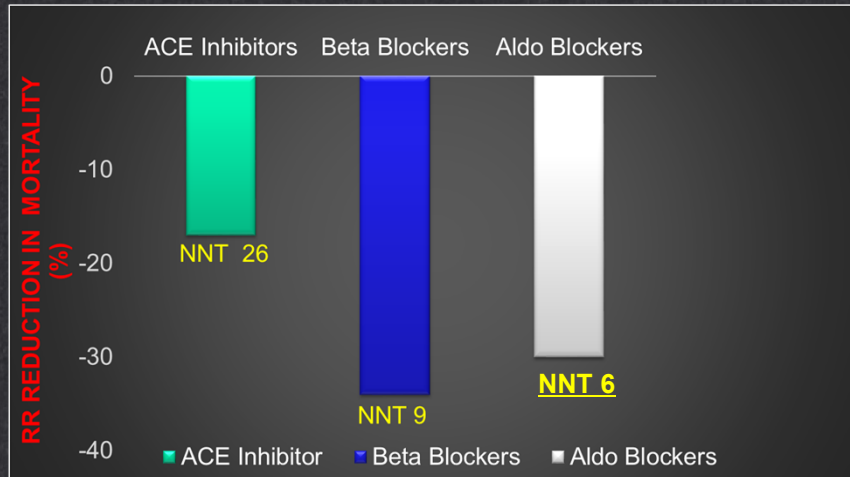
Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

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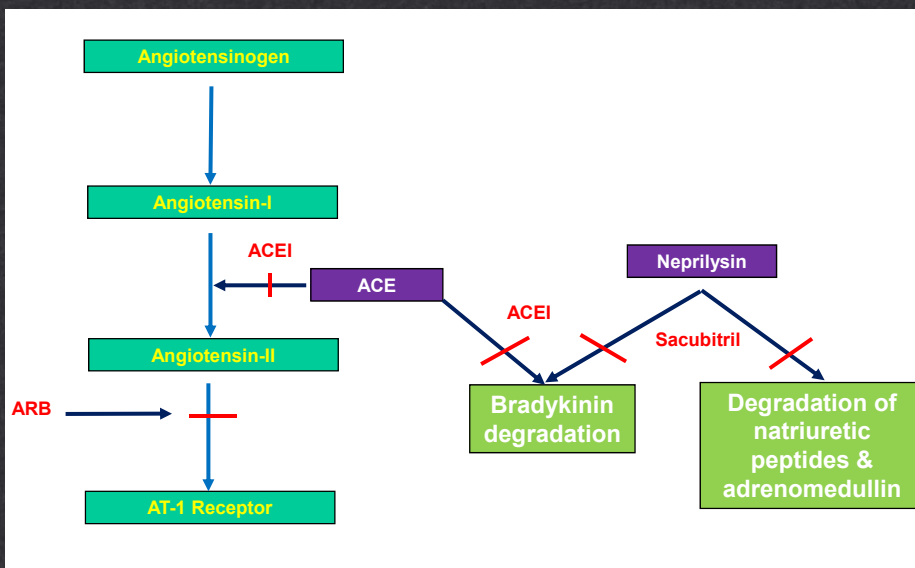


Magnitude of Benefit in RCTs

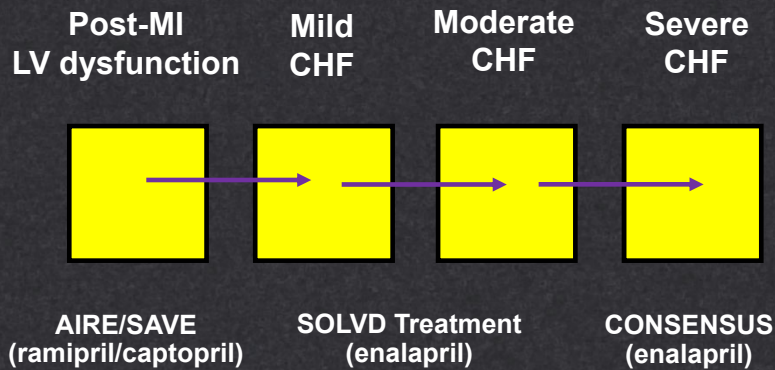


Yancy et al. Circulation, 2013;128(16): 1810-52.

Renin-Angiotensin Pathway



Renin Angiotensin Antagonism



Managing Heart Failure with ACE Inhibitors

- Indication – Symptomatic/asymptomatic pts with EF \leq 40%
- No difference among ACEI regarding Sx / survival.
- When initiating therapy, start at low dose and optimize volume status.
- Change in salt/water balance will exaggerate or attenuate clinical response.
- Expect early rise in creatinine of 10-20%; greater initial increase in creatinine in CRI.
- Creat. increase > 0.3 mg/dl seen in 15-30% with severe HF;
- 5-15% with mild-moderate HF.

ACE Inhibitors – Adverse Effects

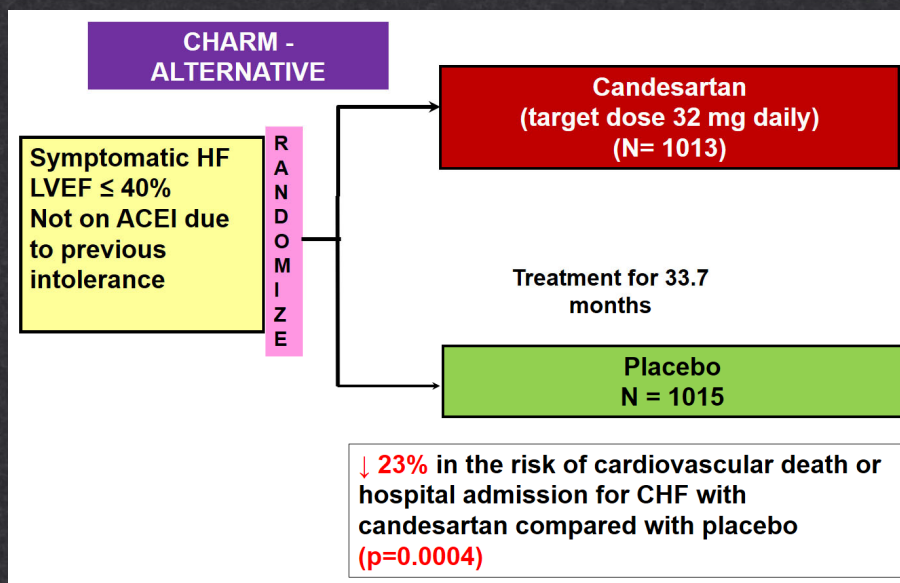
Related to angiotensin suppression:

- **Hypotension** – severe postural symptoms, worsening renal function, blurred vision, syncope.
- **Worsening renal function** –
 - 5-10% mild to moderate HF, 15-30% severe HF.
 - Risks greater with NSAID's, RAS.
 - Try to reduce diuretic first.
- **Potassium retention** – seen frequently in those with renal disease and DM

Related to kinin production:

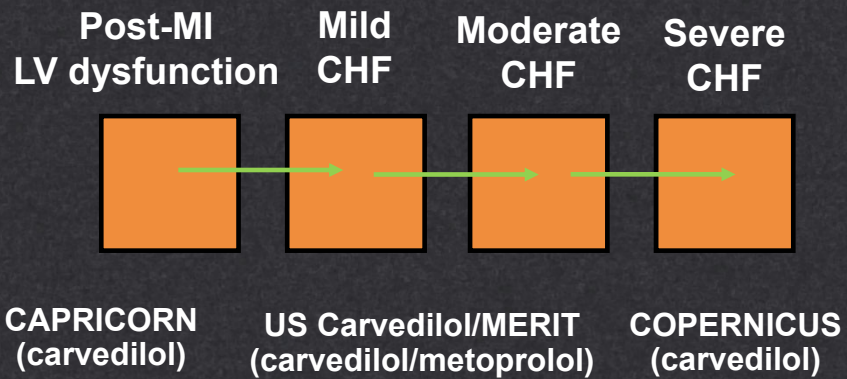
- **Cough** (5-10%)
- **Angioedema** (1%)

ARBs in Patients Not Taking ACE Inhibitors:



Granger et al. Lancet 2003; 362: 772-776

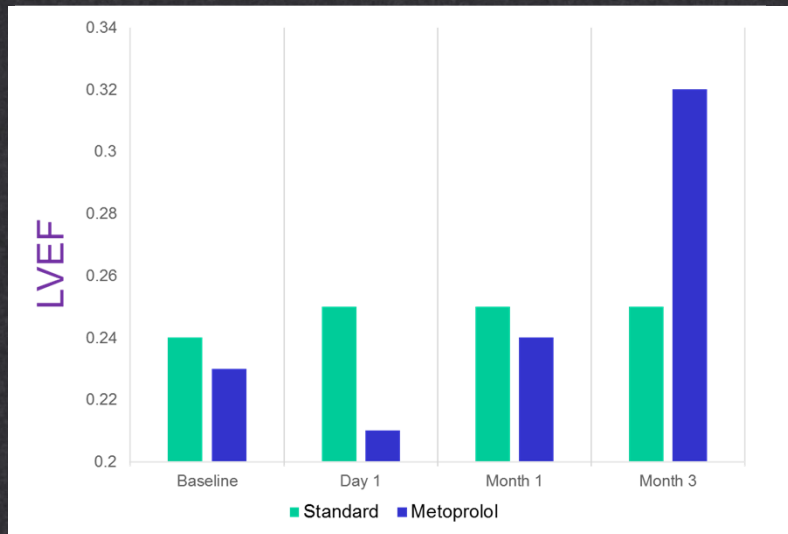
Beta- receptor Antagonism



Not all β - Blockers improve survival

Study	Drug	Target Dosage(mg)	Outcome
CIBIS 2	Bisoprolol	10 QD	↓34% mortality
MERIT-HF	Metoprolol succinate	200 QD	↓34% mortality
COPENICUS	Carvedilol	25 BID	↓35% mortality
BEST	Bucindolol	100 BID	Not significant
SENIORS	Nebivolol	10 QD	Not significant

Impact of Beta-blocker on Ejection Fraction



Hall et al JACC 1995; 25(5): 1154-1161

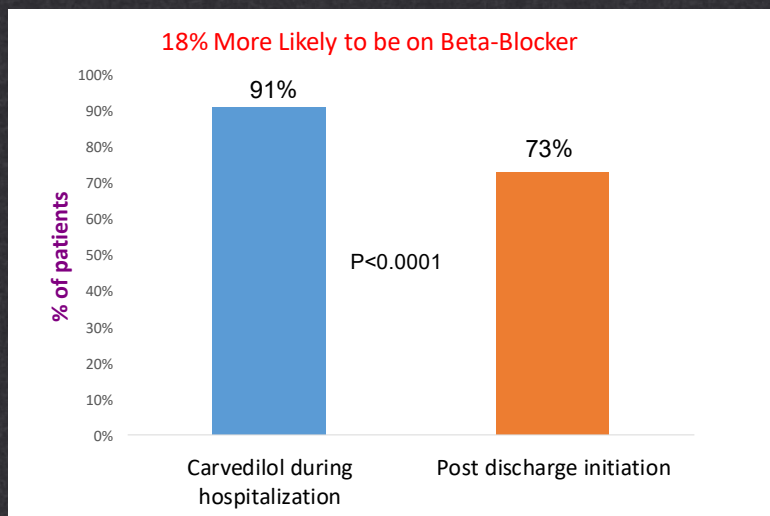
Managing Heart Failure with Beta-blockers

- Indication – Symptomatic/asymptomatic pts with EF \leq 40%
- Initiate at low dose when patient is stable
- Use drugs shown to be beneficial in studies
- Up-titrate gradually, generally \geq 2 week intervals
- Goal is target dose achieved in clinical trials
- Start in the hospital if intravenous inotropic or vasoactive medications were not used

Beta-blockers -Contraindications

- Decompensated patient
- Cardiogenic shock
- Fluid overload
- Symptomatic bradycardia/ high degree heart block (without pacemaker)
- Symptomatic hypotension

IMPACT-HF - Beta blocker at 60 days



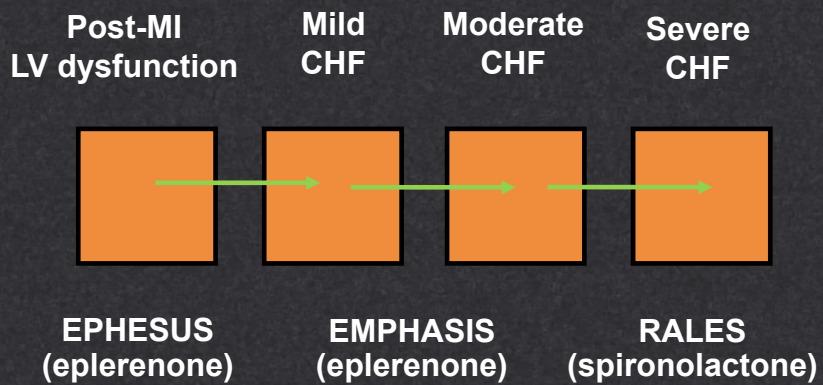
Gattis et al. JACC 2004; 43(9): 1534-1541

Aldosterone Antagonism

Study	Drug	Patient description	Outcome
RALES	Spirolactone	NYHA FC III-IV	↓30% mortality
EPHESUS	Eplerenone	Post MI HF	↓15% mortality
EMPHASIS	Eplerenone	NYHA FC II	↓24% mortality

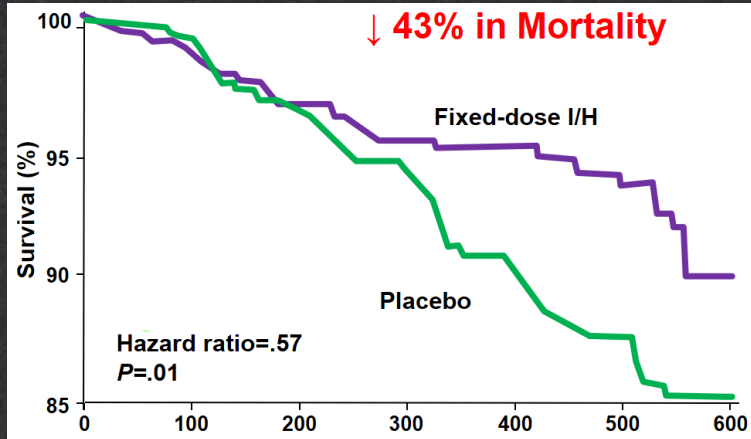
Pitt et al. NEJM 1999
Pitt et al. NEJM 2003
Zannad et al. NEJM 2011

Aldosterone Antagonism



Hydralazine/Isosorbide Dinitrate A-HeFT All Cause Mortality

AA HF
patients with
LVEF $\leq 35\%$
(or)
 $<45\%$ +
LVDD >6.5



	Days Since Baseline Visit Date						
Fixed-dose I/H	518	463	407	359	313	251	13
Placebo	532	466	401	340	285	232	24

Taylor AL, et al. *N Engl J Med*. 2004;351:2049-2057.

Selecting an ACE inhibitor

Selecting a diuretic

Sacubitril-Valsartan (ARNi)

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Neprilysin

- Enzyme that degrades several endogenous vasoactive compounds
 - Natriuretic peptides
 - Bradykinin
 - Adrenomedullin
- Inhibition of neprilysin increases levels of these substances
 - Vasodilation
 - Natriuresis
 - Diuresis

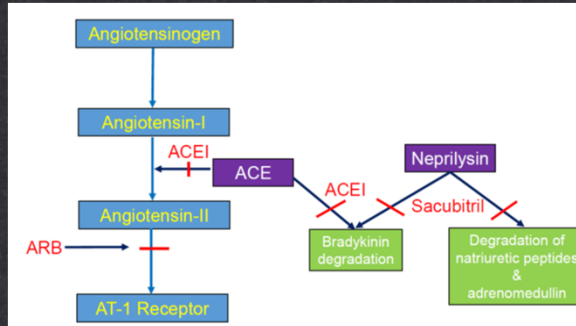
Neprilysin

- Inhibiting neprilysin was a therapeutic target for several other compounds
- Combination neprilysin and ACE inhibitor (Omapatrilat)
 - Promising, but associated with severe angioedema
 - Angioedema d/t inhibition of 3 enzymes involved in bradykinin degradation
 - ACE
 - Neprilysin
 - Aminopeptidase P

Fryer RM, et al. Br J Pharmacol 2008

Sacubitril-valsartan

- Combo of neprilysin inhibitor sacubitril and ARB valsartan
- Designed to minimize risk of angioedema by only blocking 1 bradykinin degrading enzyme



PARADIGM-HF

- 8442 patients
- LVEF \leq 40%
- NYHA II-IV
- Randomized to sacubitril-valsartan (200 mg – equivalent to valsartan 160 mg BID) or enalapril 10 mg BID
- Primary outcome was composite CV death or first HF hospitalization
- Stopped early (median follow up 27 months) because of benefit seen in interim analysis

McMurray J, et al. NEJM 2014

PARADIGM-HF: Baseline Characteristics

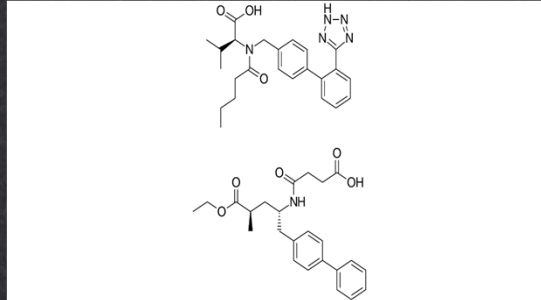
	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

PARADIGM-HF: Results

- Sacubitril-valsartan reduced primary endpoint by 20%
 - NNT = 21
- Secondary endpoints
 - 20% reduction in CV death
 - 21% reduction in HF hospitalization
 - 16% reduction in all cause mortality

Sacubitril-Valsartan

- Approved by the FDA July 7, 2015
- “Entresto”
- NYHA Class II-IV
- $EF \leq 40\%$
- Used in place of ACE or ARB
- Guidelines: IB indication for patients with HFrEF to reduce morbidity and mortality



By Vaccinationist - Own work, Public Domain,
<https://commons.wikimedia.org/w/index.php?curid=41435503>

Sacubitril-Valsartan: Contraindications

- Patients with history of angioedema due to ACE or ARB
- Pregnancy
- Do not use concurrently with ACE - hold for 36 hours after switching from ACE
- Avoid using with another ARB (i.e. avoid dual ARB therapy)

Sacubitril-Valsartan: Dosing

- Patients previously taking equivalent > 10 mg/day enalapril or > 160 mg/day valsartan
 - Starting dose 49/51 mg BID
 - Double dose (as tolerated) after 2-4 weeks to target dose 97/103
- Patients previously taking low dose (or no) ACE or ARB
 - Starting dose 24/26 mg BID
 - Double dose (as tolerated) q 2-4 weeks to target 97/103

Sacubitril-Valsartan: Dosing

- Severe renal impairment (eGFR < 30mL/min/1.73m²)
 - Starting dose 24/26 mg BID and titrate as tolerated
- Moderate hepatic impairment (Child-Pugh B)
 - Starting dose 24/26 mg BID and titrate as tolerated
- Severe hepatic impairment
 - Use not recommended

PIONEER-HF

- Initiation of sacubitril-valsartan in ADHF hospitalized pts
- 881 patients randomized: sacubitril-valsartan or enalapril
 - LVEF $\leq 40\%$
 - NT pro-BNP ≥ 1600 pg/mL or BNP ≥ 400 pg/mL
 - Enrolled within 24 hrs-10 days of presentation
 - Hemodynamically stable (no increase in diuretics or use of inotropes)
- Primary outcome: Change in the NT-proBNP concentration from baseline through weeks 4 and 8

Velazquez EJ, et al. NEJM 2019

PIONEER-HF

- Baseline characteristics
 - Mean age 61
 - 72% male
 - 36% black
 - First diagnosis of HF: 34.4%
 - 52% not on ACE/ARB at admission
 - Median SBP: 118 mmHg
 - Median hospitalization 5.2 days

PIONEER-HF

- Greater BNP reduction in sacubitril-valsartan group
 - % change: -46.7% vs. -25.3%
 - Ratio of change with sacubitril-valsartan vs. enalapril 0.71; 95% CI, 0.63 to 0.81; $P < 0.001$
 - Reduction evident as early as 1 week

PIONEER-HF

- Rates of worsening renal function, hyperK, and symptomatic hypotension did not differ significantly between groups
- 1 angioedema in sacubitril-valsartan vs 6 in enalapril group (all in black patients)
- Rate of drug discontinuation d/t adverse events did not differ

UK HARP III Trial

- United Kingdom Heart and Renal Protection-II
- 414 pts with eGFR 20-60 ml/min/1.73 m² randomized to sacubitril/valsartan 97/103 vs irbesartan 300
- Primary outcome: measured GFR at 12 months

Haynes R, et al. Circulation 2018

UK HARP III Trial

- Results
 - Baseline GFR: 34.0 and 34.7
 - At 12 months, no difference in GFR (29.8 and 29.9)
 - No difference in urinary albumin:creatinine ratio
 - Sacubitril/valsartan reduced
 - SBP by 5.4 mmHg
 - DBP by 2.1 mmHg
 - Troponin I by 16%
 - BNP by 18%

Haynes R, et al. Circulation 2018

PRIME Study

- 118 pts with chronic functional MR
- Randomized to sacubitril/valsartan or valsartan (in addition to standard GDMT)
- Primary endpoint: change in effective regurgitant orifice area at 12 months
- Results:
 - EROA -0.058 in sacubitril/valsartan vs -0.018 in valsartan ($P=0.032$)
 - Regurg volume decreased (mean difference -7.3 mL, $P=0.009$)
 - No significant difference in change in BP btwn groups

Kang DH, et al. Circulation 2019

Sacubitril-Valsartan

- Effect on ventricular arrhythmias
- 120 patients, NYHA II-IV, $EF \leq 40\%$, remote monitoring
 - For 9 months received ACE/ARB, bblocker, and aldosterone antagonist
 - ACE/ARB then changed to ARNI and followed 9 months
 - ARNI
 - ↓ NSVT (5.4 ± 0.5 vs 15 ± 1.7 in ACE/ARB; $P < .002$)
 - ↓ sustained VT and ICD shocks (0.8% vs 6.7% in ACE/ARB; $P < .02$)
 - ↓ PVCs/hr (33 ± 12 vs 78 ± 15 in ACE/ARB; $P < .0003$)
 - ↑ biventricular pacing ($95\% \pm 6\%$ to $98.8\% \pm 1.3\%$; $P < .02$)

De Diego, et al. Heart Rhythm 2017

Ivabradine

- Selective inhibitor of sinoatrial pacemaker modulating “f-current” (If)
- Slows the sinus heart rate
- Mechanism of ivabradine in HFrEF likely due to heart rate reduction

Dobre D, et al. Eur J Heart Fail 2014

SHIFT Trial

- 6558 patients
- LVEF $\leq 35\%$
- Sinus rhythm and resting HR ≥ 70 bpm
- Randomized to ivabradine or placebo
- Primary endpoint: composite CV death or HF hospitalization
- Median follow-up 23 months

Swedberg K, et al. Lancet 2010

SHIFT Trial: Baseline Characteristic

	Ivabradine N=2052	Placebo N=2098
Mean age, years	60	60
Male, %	77	77
BMI, kg/m ²	28	28
Mean HF duration, years	3.4	3.4
HF, ischemic cause, %	66	65
NYHA Class III, %	50	51
NYHA Class IV, %	2	2
Mean LVEF, %	28.7	28.5
Mean HR, bpm	84.3	84.6

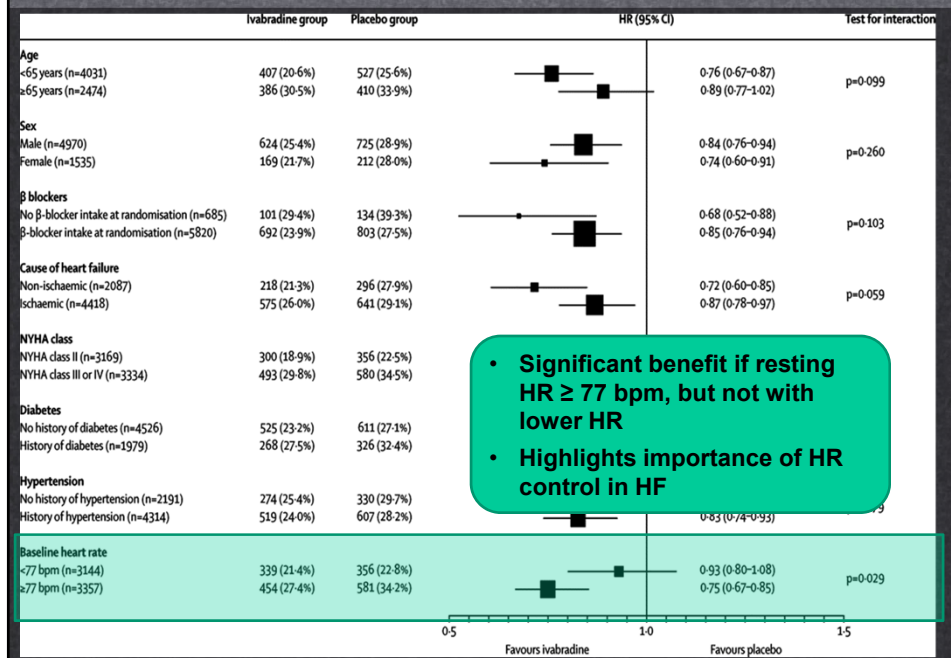
SHIFT Trial: Baseline Characteristics

GDMT	Ivabradine N=2052	Placebo N=2098
B-blocker, %	87	87
At least ½ target dose	55	56
At target dose	26	26
ACEi / ARB, %	77	77
Diuretis, %	28	28
Aldosterone antagonists, %	3.4	3.4

SHIFT Trial: Results

- Heart rate reduction
 - 28 days: HR ↓ 10.9 bpm
 - 1 yr: HR ↓ 9.1 bpm
 - Study end: HR ↓ 8.1 bpm
- 24% reduction in primary end-point in ivabradine group
- Results largely d/t ↓ HF hospitalization (HR 0.74, 95% CI 0.66-0.83) and ↓ HF death (HR 0.74, 95% CI 0.58-0.94)

SHIFT Trial: Results



Ivabradine

- Approved by the FDA on April 15, 2015
- “Corlanor”
- Stable HF with LVEF $\leq 35\%$
- Sinus rhythm with resting HR ≥ 70 bpm
- Either on max tolerated dose of β -blocker or have contraindication to β -blockers
- Not a full or partial substitute for β -blockade
- Guidelines: IIA indication in HFrEF patients on max GDMT with HR > 70

Ivabradine: Contraindications

- Acute decompensated heart failure
- Hypotension (BP $< 90/50$)
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block
- Patients who are pacemaker dependent
- Severe hepatic impairment
- In combo with strong CYP3A4 inhibitors

Other Ivabradine Data in HF

- **ETHIC-AHF**
 - Early co-administration of ivabradine and BB versus BB alone in hospitalized HFrEF pts
 - 71 pts
 - Ivabradine added 24-48 hrs after admission
 - Significant reduction in HR at 28 days and 4 months
 - Lower BNP levels
 - Lower # of pts documented to have advanced HF functional class

Hidalgo FJ, et al. Int J Cardiol 2016

Other Ivabradine Data in HF

- **PRIME-HF (Predischarge Initiation of Ivabradine in the Management of Heart Failure)**
 - Designed to enroll 450 pts; stopped early d/t difficulty with enrollment
 - 104 pts: age 57.5 yrs, 36% women, 64% black
 - 6 months post hospitalization
 - Greater HR reduction: 10 bpm vs 0.7 bpm
 - No significant reduction in b-blocker dose
 - No hypotension or bradycardia
 - 31% pts had difficulty getting initial Rx and 58% had difficulty at some point: price, insurance decline, physician stopping drug

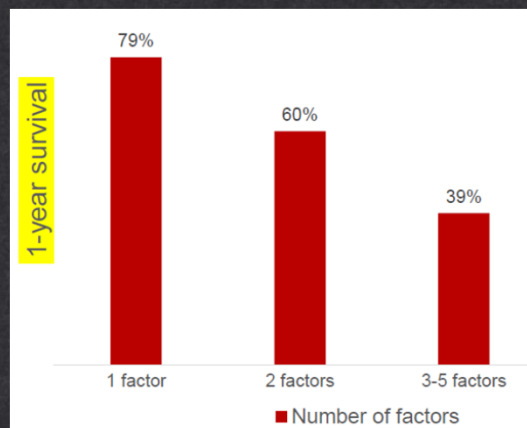
Metz, RJ, et al. Circulation 2019

Identifying Advanced Heart Failure

High risk HF patients

Criteria for referral of patients < 80 years to HF specialist

- SBP < 90 mmHg
- Creatinine ≥ 1.6
- Hb ≤ 12
- No RAS antagonist
- No β -blocker



Thorvaldsen, et al. JACC 2014.

Patient referral to HF specialist I-NEED-HELP

- I: IV inotropes
- N: NYHA IIIB/IV or persistently elevated natriuretic peptides
- E: End-organ dysfunction
- E: Ejection fraction $\leq 35\%$
- D: Defibrillator shocks
- H: Hospitalizations > 1
- E: Edema despite escalating diuretics
- L: Low blood pressure, high heart rate
- P: Prognostic medication – progressive intolerance or down-titration of GDMT

Yancy, et al. JACC 2017