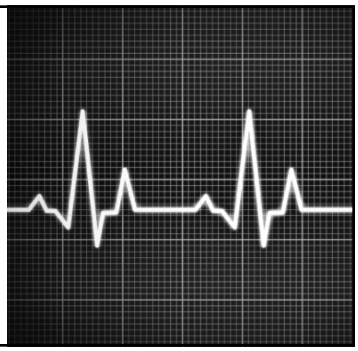
Cardiovascular Pharmacotherapy for Heart Failure Management

AN UPDATE OF THE LATEST RECOMMENDATIONS AND DATA

By: Debby Caraballo, PharmD, PhC, BCPS, AQ-Cardiology
Balloon Fiesta Symposium, Albuquerque, NM
September 9th, 2018



Objectives

- Briefly describe HF clinical syndrome and definitions
- Review HFrEF medication therapy
- Review Updated HF Guideline recommendations
- Review supportive data for key recommendations
- Briefly review drugs that can exacerbate HF

Heart Failure – A clinical syndrome

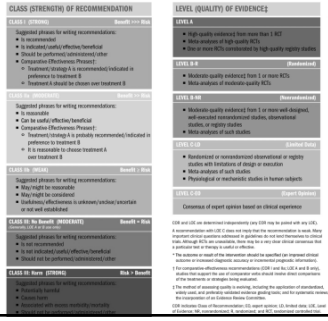
- Typical *symptoms* that may be accompanied by *signs*
- …caused by a structural and/or functional cardiac abnormality
- …resulting in reduced CO and/or elevated intracardiac pressures at rest or during stress
- Pt can present with asx structural or functional cardiac abnormalities (systolic or diastolic LV dysfunction)
- Important to start tx early

Heart Failure- Classification

- Stage A- At risk
- Stage B- Structural damage without Sx
- Stage C- Structural damage with Sx
- Stage D- End-stage

- NYHA Class I- no limitation
- NYHA Class II- limitation with ordinary activity
- NYHA Class III- limitation with less than ordinary activity
- NYHA Class IV- Sx at rest/end-stage

Classification of Recommendations and Levels of Evidence



Clyde W. Yancy et al. Circulation. 2017;136:e137-e161

Key Updates

- Biomarkers
- Pharmacotherapy
  - HFrEF
  - HFpEF
- Nutritional Supplements
- Anemia
- HTN (New section!)
- Sleep Disorders

Biomarkers

- Well established role for
  - Assist in Dx or exclusion of HF as a cause of sx in chronic HF (ambulatory) or ADHF
- Role in population screening is emerging
  - Low diagnostic sensitivity in obese
- Baseline levels useful in admissions

Pharmacological Treatment for Stage C HHrEF

ANGIOTENSIN-NEPRILYSIN INHIBITOR

Pharmacological Treatment for Stage C HF With Reduced EF

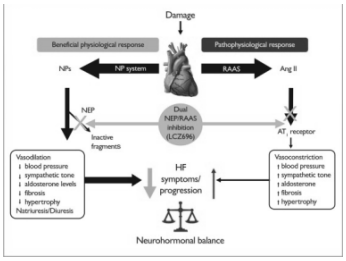
Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI

COR	LOE	Recommendations	Comment/ Rationale
I	ACE-I: A ARB: A ARNI: B-R	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.	NEW: New clinical trial data prompted clarification and important updates.

ARNI

- Angiotensin Receptor-Neprilysin Inhibitor
- Sacubitril-Valsartan
- MOA- Promote natriuretic response

ARNI- Mechanism of Action

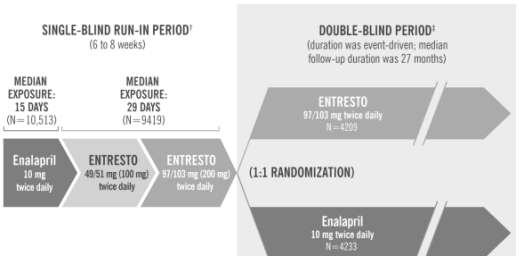


R.R. Dargad, et al. Sacubitril/valsartan: A novel angiotensin receptor neprilysin inhibitor, Indian Heart J (2018), In press. https://doi.org/10.1016/ihj.2018.01.002

PARADIGM-HF

- McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004
- RCT
- N= 8442
- EF 40% or less, NYHA Class II-IV
- Enalapril 10 mg BID v. Sacubitril-valsartan 200 mg BID
  - Controversy; Data supports this dose
  - Average dose: 18.9 mg/day (CONSENSUS= 16.6)

PARADIGM-HF Study Design



https://www.entrestohcp.com/paradigm-hf-clinical-trial. Accessed 7/1/18.

PARADIGM-HF, continued…

- Primary Endpoint-
  - Composite of death from CV causes OR a 1st hospitalization for HF
- Secondary Endpoints:
  - Time to death from any cause
  - Change from BL to 8 months in clinical summary score
  - Time to N.O. Afib
  - Time to 1st occurrence of a decline in renal funciton (ESRD or dec in eGFR 50% or more than 30ml/min).

PARADIGM-HF- Results

- BB (93%), Diuretic (80%), MRA (54-57%)
- 20% decrease in mortality (HR 0.80; CI- 0.73 to 0.87; P<0.001)
- (SOLVD trial we have a 16% dec in mortality) (N= 2569, dec 16% in mortality)
- NNT = 21 (death from CV cause or hospitalization)
- NNT = 32 (death from CV causes)

Guideline Directed Medical Therapy

Benefit Demonstrated in RCTs

GDMT	RR Reduction in Mortality (%)	NNT for Mortality Reduction (Standardized to 36 mo)	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

***Circulation.* 2013;128:e240-e327**

Pointers

- Dose- 50 mg BID up to 200 mg BID
- Dosage forms: tablet 24/26 mg, 49/51 mg, 97/103 mg
- Valsartan in Entresto is more bioavailable that other marketed tablet formulations
- Entresto 24/(26) mg= valsartan 40 mg
- Entresto 49/(51) mg= valsartan 80 mg
- Entresto 97/(103) mg= valsartan 160 mg

ACE CONVERSION CHART

LISINOPRIL	ENALAPRIL	SACUBITRIL-VALSARTAN
5	5	50
10	10	100
20-40	20-40	200

ACE CONVERSION CHART

LISINOPRIL	ENALAPRIL	SACUBITRIL-VALSARTAN
5 mg/day	5 mg/day	50 mg BID
10 mg/day	100 mg/day	100 mg BID
20-40 mg/day	20-40 mg/day	200 mg BID

ARB CONVERSION CHART

LOSARTAN	VALSARTAN	SACUBITRIL-VALSARTAN
25 mg/day	40 mg BID	50 mg BID
50 mg/day	80 mg BID	100 mg BID
100-150 mg/day	160 mg BID	200 mg BID

Table 3. Drugs Commonly Used for HFrEF (Stage C HF)

Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
ACE inhibitors			
Captopril	6.25 mg TID	50 mg TID	122.7 mg QD
Enalapril	2.5 mg BID	10–20 mg BID	16.6 mg QD
Fosinopril	5–10 mg QD	40 mg QD	N/A
Lisinopril	2.5–5 mg QD	20–40 mg QD	32.5–35.0 mg QD
Perindopril	2 mg QD	8–16 mg QD	N/A
Quinapril	5 mg BID	20 mg BID	N/A
Ramipril	1.25–2.5 mg QD	10 mg QD	N/A
Trandolapril	1 mg QD	4 mg QD	N/A
ARBs			
Candesartan	4–8 mg QD	32 mg QD	24 mg QD
Losartan	25–50 mg QD	50–150 mg QD	129 mg QD
Valsartan	20–40 mg BID	160 mg BID	254 mg QD
ARNI			
Sacubitril/valsartan	49/51 mg BID (sacubitril/valsartan) (therapy may be initiated at 24/26 mg BID)	97/103 mg BID (sacubitril/valsartan)	375 mg QD; target dose: 24/26 mg, 49/51 mg OR 97/103 mg BID

Pharmacological Treatment for Stage C HFrEF

IVABRADINE

Pharmacological Treatment for Stage C HF With Reduced EF

Ivabradine

COR	LOE	Recommendations	Comment/ Rationale
IIa	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, 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.	NEW: New clinical trial data.

Ivabradine

- MOA- Inhibits I_f current in SA node to reduce HR
- Indication: reduce risk of hospitalization for worsening HF in:
  - Pts with stable, Sx HFrEF (EF </= 35%)

AND

- Who are in SR with resting HR >/= 70 bpm

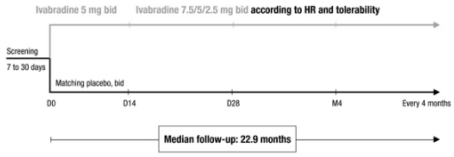
AND

- Who are on maximally tolerated BB tx or have a CI to BB tx

SHIFT Trial

- Raised resting HR is a RF for mortality and CV outcomes *(Diaz A. et al. Eur Heart J 2005, Wilhelmsen L, et al. Eur Heart J 1986)*
- Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376:875–85.
- RCT, DB
- N= 6558
- EF 35% or lower, Sx HF, SR with HR >/= 70 bpm , admission for HF w/in previous year, and on stable background tx including BB (if tolerated)
- Median f/u 22.9 months

SHIFT- Trial Design



SHIFT- Results

- Primary endpoint - Composite of cardiovascular death or hospital admission for worsening heart failure
  - Decreased by 18%
- 26% decrease in admissions for worsening HF

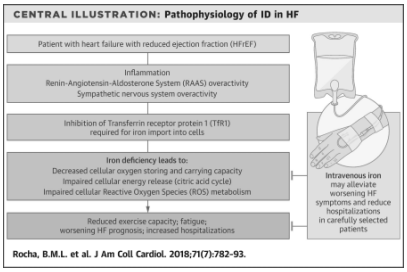
Pharmacological Treatment for Stage C HF With Reduced EF

IRON DEFICIENCY

Iron Deficiency and HFrEF

COR	LOE	Recommendations	Comment/ Rationale
IIb	B-R	In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and QoL.	NEW: New evidence consistent with therapeutic benefit.
III: No Benefit	B-R	In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality.	NEW: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit.

IRON DEFICIENCY AND HFrEF



ID in HFrEF Data

- FAIR-HF
- Subanalysis of FAIR-HF
  - Treatment of ID with FCM in HF is equally efficacious irrespective of anemia.
  - Fe status should be assessed in Sx HF both with and w/o anemia and tx of ID should be considered.
- COHNFIRM-HF
  - Multi-center DB, PCT. N= 304. EF </= 45%, elevated natriuretic peptides and ID.
  - Treatment of Sx, ID HF patients with FCM over a 1yr period resulted in sustainable improvement in functional capacity, sx, and QoL and
  - May be associated with risk reduction of hospitalization for worsening HF

Pharmacological Treatment for Stage C HFpEF

MINERALOCORTICOID RECEPTOR ANTAGONISTS

Pharmacological Treatment for Stage C HFpEF

COR	LOE	Recommendations	Comment/ Rationale
IIb	B-R	In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.	NEW: Current recommendation reflects new RCT data.
IIb	B	The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF.	2013 recommendation remains current.

TOPCAT-HF

- Spironolactone for Heart Failure with Preserved Ejection Fraction. Pitt B, et al. N Eng J Med 2017;370:1383-92.
- RCT, DB
- N=3445
- HFpEF EF >/= 45%
- MRA (spironolactone) v. PLCB
- 1˚ endpoint- Composite death from CV causes, aborted CV arrest, or hospitalization for the management of HF.
- Mean f/u 3.3 years
- Clinically significant reduction in incidence of hospitalization only

TOPCAT-HF, cont.

- ADE- kyperkalemia, increased SrCr
- With frequent monitoring, there was no significant differences in the incidence of serious ADE, SrCr > 3 mg/dl, or HD.

Pharmacological Treatment for Stage C HFpEF

COR	LOE	Recommendations	Comment/ Rationale
III: No Benefit	B-R	Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HF*p*EF is ineffective.	NEW: Current recommendation reflects new data from RCTs.
III: No Benefit	C	Routine use of nutritional supplements is not recommended for patients with HF*p*EF.	2013 recommendation remains current.

Prevention Startegies

TREATING HTN TO REDUCE THE INCIDENCE OF HF

HYPERTENSION

Treating Hypertension to Reduce the Incidence of HF

COR	LOE	Recommendations	Comment/ Rationale
I	B-R	In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg.	NEW: Recommendation reflects new RCT data.

Prevention Strategies

DRUGS THAT MAY CAUSE OR EXACERBATE HEART FAILURE

Drugs that can exacerbate HF

- Drugs may cause or exacerbate HF by:
  - Causing direct myocardial toxicity;
  - Negative inotropic, lusitropic, or chronotropic effects;
  - Exacerbating hypertension;
  - Delivering a high sodium load; or
  - Drug-drug interactions (DDI) that limit the beneficial effects of HF medications

Drugs that can exacerbate HF

- *Circulation. 2016;134:e32–e69.*
- Polypharmacy = LT use of ≥5 medications
- Pts ≥ 2 medications had a 13% risk of an adverse DDI
- Pts ≥ 4 medications → 38%
- Pts ≥7 medications 82%
- Prevention of DDIs→ ↓ admissions → ↓ costs & QoL

Potassium Binders

IMPROVING ADHERENCE TO GDMT FOR HFREF WITH POTASSIUM BINDERS

Potassium Binders

- Hyperkalemia (HK) incidence higher in HF, CKD
- Drug-induced HK most commonly associated with RAAS inhibitors
- Typical management includes loop diuretics, close monitoring, discontinuation of beneficial agent → undesirable outcomes
- Sodium polystyrene sulfonate (SPS/Kayexalate) only option for decades
- High sodium content, GI ADEs, lack clinical data

Potassium Binders- Patiromer

- Patiromer sobitex calcium (patiromer)- Veltassa (Approved 2015)
- Non-absorbed oral K+-binding polymer.
- Acts primarily in distal colon (where the K+ is the highest), to increase fecal excretion (preferentially exchanges K+ for H/Na.
- Not specific for K+ (hypomagnesemia)
- OPAL-HK, AMETHYST-DN, PEARL-HF
- Dose: 8.4g q daily, Increase by increments of 8.4g q 1 week intervals to max 25.2g/d
- ADEs: HypoMg++, HypoK+ (5%), constipation, diarrhea, flatulence, nausea
- Oral medications should be administered at least 3 hours before or 3 hours after patiromer

Potassium Binders- ZS9

- Sodium zirconium cyclosilicate (ZS9)- Lokelma (Approved 2018)
- Inorganic, unabsorbable polymer of zirconium silicate
- 10X specific for potassium as patiromer
- 400 mg Na++ per 5 g dose
- HARMONIZE, Substudy in HF
- Dose: 10 g TID initially x up to 48h; chronic 5-15 g/day. Increase in 5g at 1 week intervals.
- ADEs- edema, peripheral edema, hypoK (4%)
- In general, other oral medications should be administered at least 2 hours before or 2 hours after ZS9

WRAP UP….

- https://youtu.be/aS3xaXsh6vo

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QUESTIONS?