Pharmacy Pearls

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Updates on Medication Management in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF)

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ACC/AHA Heart Failure (HF) Staging Definitions:

Treatment recommendations in this document apply specifically to **HFrEF (LVEF < 40%) – Stage C** patients

Stage A	Stage B	Stage C	Stage D
At risk for heart disease but no actual structural disease	Structural disease but no prior or current heart failure symptoms	Structural disease with past or current heart failure symptoms	End-stage disease that is refractory to medical treatment

General Treatment Algorithm (per ACC/AHA updated 2017 recommendations):

Step 1: All patients should be initiated on ACE-I/ARB AND guideline-directed Beta Blocker (BB) +/- diuretics as needed

- If patient is volume overloaded ("wet") → Initiate ACE-I/ARB first
- If patient is not volume overloaded ("dry") and has adequate resting HR (≥ 55 bpm) → Initiate BB first

Step 2: Modify therapy as needed based on clinical presentation (choices not mutually exclusive and no preferred order)

- Persistent volume overload (NYHA Class II-IV) → **Titrate** diuretics
- Persistently symptomatic and African American (NYHA Class III-IV) → **Add** hydralazine + isosorbide dinitrate
- Stable on ACE-I/ARB (NYHA Class II-III) → **Switch** to Entresto®
- eGFR > 30mL/min and K < 5.0 mEq/L (NYHA Class II-IV) → **Add** aldosterone antagonist (AA)
- HR > 70 bpm, on max-tolerated BB (or cannot tolerate BB), and in normal sinus rhythm (NYHA Class II-III) → **Add** ivabridine

Initial and Target Doses for Common HF Medications:

Class	Medication	Initial Dose	Target Dose
ACE-I	Captopril	6.25 mg TID	50 mg TID
	Enalapril	2.5 mg BID	10-20 mg BID
	Lisinopril	2.5-5 mg daily	20-40 mg daily
	Ramipril	1.25 mg daily	10 mg daily
ARB	Candesartan	4-8 mg daily	32 mg daily
	Losartan	25-50 mg daily	150 mg daily
	Valsartan	40 mg BID	160 mg BID
ARNI	Sacubitril/ Valsartan	24/26 mg BID	49/51 mg BID

Class	Medication	Initial Dose	Target Dose
BB	Bisoprolol	1.25 mg daily	10 mg daily
	Carvedilol	3.125 mg BID	25-50 mg BID
	Metoprolol XL	12.5-25 mg daily	200 mg daily
AA	Eplerenone	25 mg daily	50 mg daily
	Spironolactone	12.5-25 mg daily	25-50 mg daily
Vaso-dilators	Hydralazine	25 mg TID	75 mg TID
	Isosorbide DN	20 mg TID	40 mg TID
HCN channel blocker	Ivabridine	2.5-5 mg BID	Titrate to HR of 50-60 bpm (max = 7.5 mg BID)

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Newest HF Medications:

Angiotensin Receptor-Neprilysin Inhibitor (ARNI)

Sacubitril/Valsartan (Entresto ®)

Mechanism of Action: Sacubitril increases levels of natriuretic peptides that delay the pathogenesis and progression of HF and valsartan inhibits aldosterone release.

Cost: $631 (30-day supply, average cash price)

Benefits: Resulted in a 20% reduction in cardiovascular death and HF hospitalizations in clinical trials and is associated with clinical improvement in LVEF. Class 1 (strong) recommendation in ACC/AHA guidelines.

Limitations: Risk of angioedema, more symptomatic hypotension than patients on ACE-I, and was not studied in patients with decreased renal function.

Ideal candidates for therapy: Patients with NYHA Class II-III symptoms, who can tolerate an ACE-I/ ARB, to further reduce morbidity and mortality. Use of an aldosterone antagonist is also recommended to improve outcomes but is not a mandatory step prior to switching a patient to ARNI.

How to Switch Therapy:

Step 1: Ensure 36 hours off ACE-I, adequate BP, and eGFR > 30 mL/min

Step 2: Select starting dose

Population:	Dose:
• Low dose ACE-I/ARB • ACE-I/ARB naïve • Hepatic impairment (Child-Pugh Class B) • Elderly age (≥ 75 years)	24/26 mg BID
• Moderate or high dose of ACE-I/ARB (equivalent of ≥ 10 mg of enalapril BID or ≥ 80 mg BID of valsartan) ○ Full list of equivalent dosages available here: **ACE-I / ARB**	49/51 mg BID

Step 3: Assess tolerability in 2-4 weeks. If possible, titrate dose to target of 97/103 mg BID. Monitor BP, electrolytes, and renal function during titration and periodically thereafter.

HCN Channel Blocker

Ivabridine (Corlanor ®)

Mechanism of Action: Reduces heart rate by decreasing spontaneous pacemaker activity at the cardiac sinus node. Does not lower blood pressure.

Cost: $530 (30-day supply, average cash price)

Benefits: Resulted in a 5% (statistically significant) reduction of HF hospitalizations in clinical trials.

Limitations: Can cause bradycardia, development of atrial fibrillation, and transient blurred vision. Class IIa (moderate) recommendation in ACC/AHA guidelines.

Ideal candidates for therapy: Well-compensated patients on optimal/highest-tolerated BB therapy, in sinus rhythm, who have a persistent resting HR > 70 bpm. Highest benefit shown in patients with contraindications to BB therapy, BB doses < 50% of guideline-directed targets, and resting HR > 77 bpm at time of initiation.

How to Initiate Therapy:

Step 1: Reassess that BB therapy is adjusted to target doses or max-tolerated dose

Step 2: Select starting dose

Population:	Dose:
• Age ≥ 75 years	2.5 mg BID
• Age < 75 years	5 mg BID

Step 3: Reassess HR in 2-4 weeks and adjust dose as below. Monitor HR during titration/throughout therapy.

- HR < 50 bpm or symptoms of bradycardia → Reduce dose by 2.5 mg BID or discontinue if already at lowest dose.
- HR 50-60 bpm → Maintain current dose.
- HR > 60 bpm → Increase dose by 2.5 mg BID until at max dose of 7.5 mg BID.