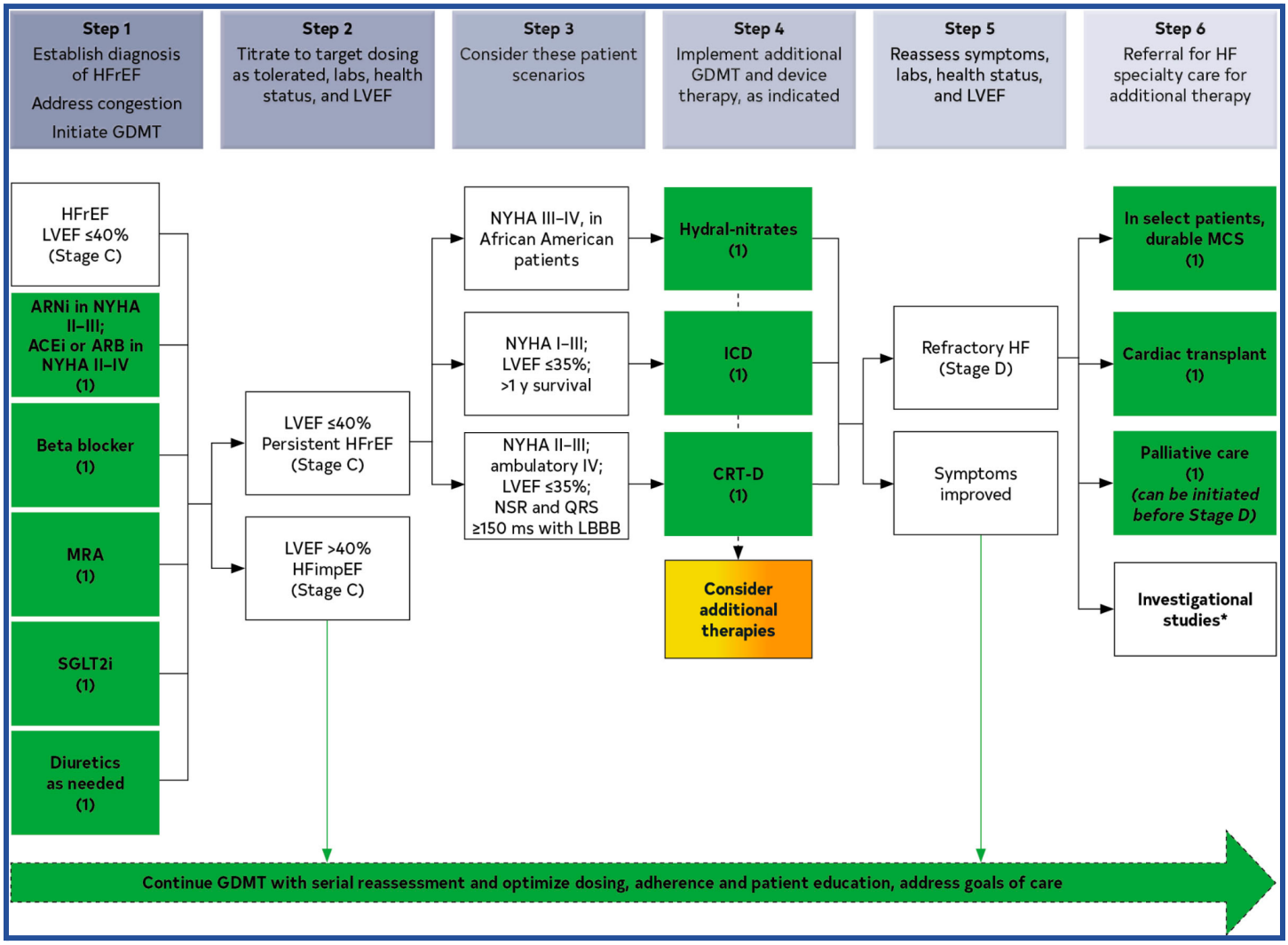
Management of HFrEF Stages C and D

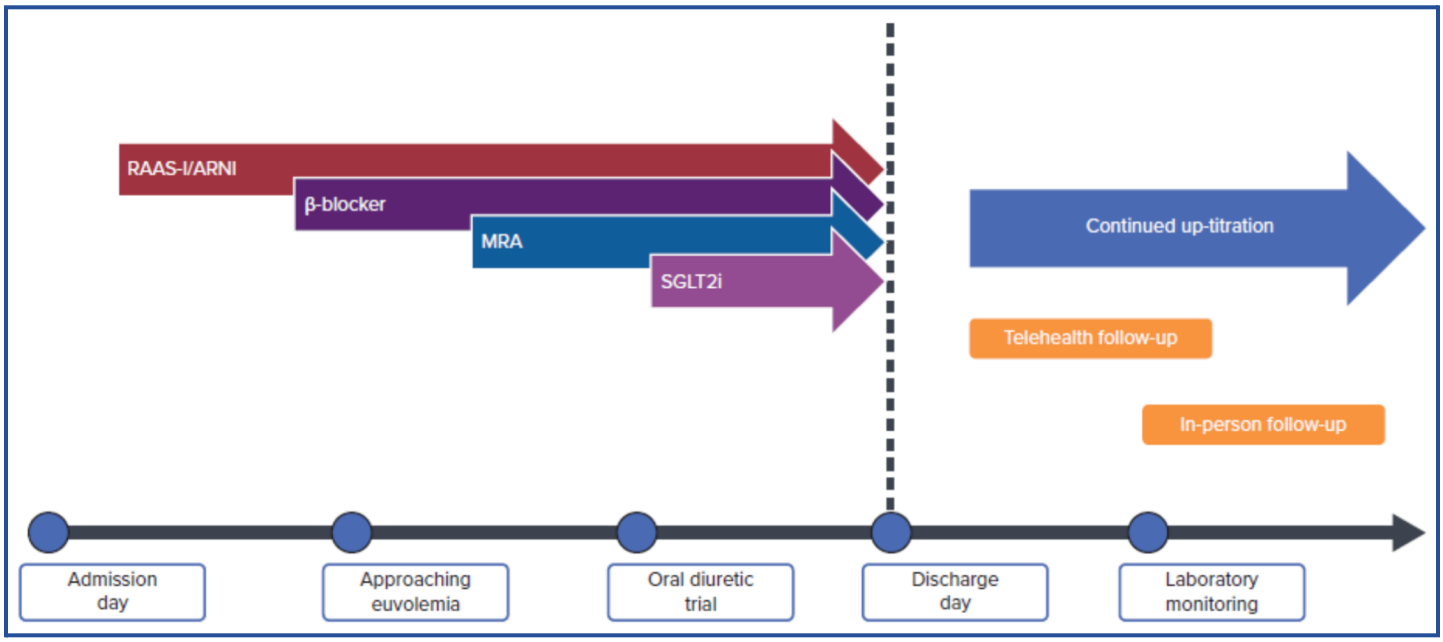


*Guidelines reference the use of alternative agents for specific populations, for this intervention the main focus will be on the four pillar medication classes

Guideline Directed Medical Therapy (GDMT):

1. Renin-angiotensin-aldosterone system inhibitors (RAAS-I)
2. Beta blockers (BB)
3. Mineralocorticoid receptor antagonists (MRA)
4. Sodium-glucose cotransporter-2 inhibitor (SGLT2i)

Initiation of GDMT:



Drug	RAAS-I / ARNI	BB	MRA	SGLT2i
Initiation Criteria	ARNI initiation: - SBP > 100 mmHg for 6 h - No use of IV vasodilators or increase in dose of IV diuretics in the preceding 6 h - No use of inotropes in the preceding 24 h - eGFR > 45 mL/min/1.73m^2 - K < 5.0 mEq/L	- No hypoxia, symptomatic hypotension, or evidence of shock	- On at least minimum dose of RAAS-I and BB - SCr < 2.5 mg/dL in men, < 2.0 mg/dL in women - K < 5.0 mEq/L - No symptomatic hypotension	- On at least minimum dose of RAAS-I and BB - eGFR > 30 mL/min/1.73m^2 - No symptomatic hypotension
Up-titration strategy	- Direct initiation of ARNI preferred strategy - If SBP 100-120 mmHg initiate sacubitril/valsartan 24/26 mg BID - If SBP > 120 mmHg initiate sacubitril/valsartan 49/51 mg BID - Double dose every 1-2 days as tolerated until target dose reach or initiation of next pillar of GDMT	- If SBP 90-120 mmHg or < 85 kg start equivalent of carvedilol 3.125 mg BID - If SBP > 120 mmHg or > 85 kg start equivalent of carvedilol 6.25 mg BID - Increase every 1-2 days as tolerated until target dose reached	- Initiate at equivalent of spironolactone 12.5 mg daily after the initiation of BBs and increase weekly	- Initiate before or after MRA, prior to discharge - No dosage increase required
Potential CI	- K > 5.5 mEq/L	- HR < 50 BPM	- K > 5.0 mEq/L - SCr > 2.5 mg/dL in men - SCr > 2.0 mg/dL in women	- T1D - eGFR < 30 mL/min/1.73m^2

*RAAS-I = renin-angiotensin-aldosterone system inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor; CI = contraindication; SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate; K = serum potassium; SCr = serum creatinine; BID = twice daily; HR = heart rate; BPM = beats per minute; T1DM = type 1 diabetes

Clinical Pearls for GDMT Medications:

Class	Recommendations	Caution	Monitoring
ACEi	- Preferred for NYHA class I - Use before ARB	- Contraindicated in patients with a history of angioedema - Use with caution in patients with hypotension, hyperkalemia, and AKI - Avoid in pregnant patients	- Monitor serum K+, SCr, and BUN at baseline - Monitor for a decrease in BP and assess symptoms prior to titrating
ARB	- Preferred for NYHA class I if unable to take ACEi	- Use with caution in patients with hypotension, hyperkalemia, and AKI - Avoid in pregnant patients	- Monitor serum K+, SCr, and BUN at baseline - Monitor for a decrease in BP and assess symptoms prior to titrating
ARNi	- Preferred for NYHA class II-IV - If switching from standard doses of ACEi or ARB then start at 49/51 mg BID dosing	- Cannot be given within 36 hours of an ACEi - No washout period when switching from an ARB - Use with caution in patients with hypotension, hyperkalemia, and AKI - Avoid in pregnant patients - If SBP is < 100 mmHg throughout hospitalization, prior to discharge, trial on equivalent of valsartan 20 mg BID or lisinopril 5 mg once daily with intent to switch to ARNI when tolerated	- Monitor serum K+, SCr, and BUN at baseline - Monitor for a decrease in BP and assess symptoms prior to titrating
BB	- All patients with HFrEF unless contraindicated (e.g., 2nd or 3rd heart block) - Convert metoprolol tartrate to succinate	- Use beta$_1$ selective for asthma or severe reversible airway disease patients - Careful in severe bradycardia - Younger and heavier patients may tolerate more aggressive dosing	- Monitor for significant decrease in HR and BP - Assess symptoms and titrate to target dose if tolerable - Hold if HR < 60 bpm, reduce dose if needed to last tolerable dose
MRA	- NYHA class II-IV - Prior to initiation, K+ must be ≤ 5 mEq/L and eGFR ≥ 30 mL/min/1.73m2	- Caution when used in combination with other medications that increase potassium levels - Caution in dehydrated states - Avoid in pregnant patients	- Monitor serum K+, SCr, and BUN at baseline - Monitor for a decrease in BP and assess symptoms/tolerability
SGLT2i	- NYHA class II-IV - Recommended in CKD - For initiating look at eGFR: - Empagliflozin must be ≥ 25 mL/min/1.73m^2	- Consider adjusted diuretic when initiating if hypovolemic - Avoid in patients on dialysis and in pregnancy - T2DM patients on insulin or sulfonylurea may require reduced insulin doses and close glycemic monitoring - Immediate reduction in eGFR by 4-6 mL/min/1.73m^2 is expected and not harmful	- Monitor SCr, BUN, and Na+ - Signs of yeast or urine infections - Glucose levels in diabetic patients

*NYHA = New York Heart Association; K+ = serum potassium; SCr = serum creatinine; BUN = blood urea nitrogen; BP = blood pressure; AKI = acute kidney injury; HR = heart rate; eGFR = estimated glomerular filtration rate

Dosing and Titration:

Medication Class	Generic Name	Initial Dose	Target Doses	Titrating Comments
ACEi	Captopril	6.25 mg TID	50 mg TID	Titrate every few days in-hospital to reach goal dose
	Enalapril	2.5 mg BID	10 to 20 mg BID	
	Lisinopril	2.5 to 5 mg QD	20 to 40 mg QD	
	Ramipril	1.25 to 2.5 mg QD	10 mg QD	
ARB	Valsartan	20 to 40 mg BID	160 mg BID	Titrate every few days in-hospital to reach goal dose
	Losartan	25 to 50 mg QD	50 to 150 mg QD	
ARNi	Sacubitril/valsartan	24/26 mg BID	97/103 mg BID	Titrate every week
Beta-blocker	Bisoprolol	5 mg QD	10 mg QD	Titrate every 2 weeks
	Carvedilol Immediate Release	3.125 mg BID	≤ 85 kg 25 mg BID or > 85 kg 50 mg BID	
	Carvedilol Extended Release	10 mg QD	80 mg QD	
	Metoprolol succinate	12.5 to 25 mg QD	200 mg QD	
MRA	Eplerenone	25 mg QD	50 mg QD	Titration often not required, may be seen for diuretic effect
	Spironolactone	12.5 to 25 mg QD	25 to 50 mg QD	
SGLT2	Empagliflozin	10 mg QD		Titration not required

Medications to avoid and recommend discontinuation of:

- Non-steroidal anti-inflammatory drugs (NSAIDs): aspirin, meloxicam, sulindac, ibuprofen, naproxen, ketorolac, celecoxib
- Cold and cough medications with pseudoephedrine and phenylephrine
- Alka-seltzer
- Thiazolidinediones (TZDs): pioglitazone
- Non-dihydropyridine calcium channel blockers (Non-DHP CCBs): cardizem and verapamil
- Always question herbals and natural supplements

Pharmacy GDMT Optimization Study Criteria:

- Inclusion criteria:
  a. ≥ 18 yo
  b. LVEF ≤ 40% in last 12 months
  c. Primary cause of hospitalization is HF exacerbation
- Exclusion criteria:
  a. Prior heart transplant or current LV assistance device
  b. Terminal illness other than HF, such as a malignancy
  c. End-stage HF on inotropes
  d. Congenital heart disease
  e. Patients with chronic liver disease, classified by Child-Pugh Class C
  f. Requiring hemodialysis or eGFR < 30 mL/min/1.73m^2
  g. Documented history of angioedema
  h. Length of hospital stay < 24 hours
  i. Pregnant

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2. Neal M Dixit, Shivani Shah, Boback Ziaeian, Gregg C Fonarow, Jeffrey J Hsu, Optimizing Guideline-directed Medical Therapies for Heart Failure with Reduced Ejection Fraction During Hospitalization, *US Cardiology Review 2021;15:e07.* https://doi.org/10.15420/usc.2020.29

3. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 ACC/AHA/HFSA guideline for the management of heart failure. *J Card Fail.* 2022;28(5):e1-e167. doi:10.1016/j.cardfail.2022.02.010