Guideline-Directed Medical Therapy (GDMT)
Titration for Heart Failure with Reduced Ejection Fraction (HFrEF):

What is the type?

1. HFrEF = Ejection Fraction <40% (reduced ejection fraction)
2. HFpEF= Ejection Fraction >50% (preserved ejection fraction)
3. HFmrEF= Ejection Fraction 40-49% (mid-range ejection fraction)
4. HFrecEF= Heart failure with recovered ejection fraction to >40%.

Heart failure is a complex disease caused by a variety of disorders. New diagnosis of HF should be followed with consultation to cardiology for evaluation of etiology. Effective management depends on correct etiology diagnosis. ACC/AHA guidelines are used to evaluate both HFpEF and HFrEF etiology. Etiology may take time to determine, but GDMT for HFrEF commences upon diagnosis.

Treatment HFrEF:

Principles to titrations

1. Know target doses of HFrEF medications used in randomized trials. Common ones listed below.
2. Low blood pressures alone are not a contraindication to using HFrEF medications or titrating HFrEF medications. Follow symptoms and end-organ dysfunction to determine tolerance.
3. Beta blockers should be titrated to target doses; ACE/ARB/angiotensin receptor-neprilysin inhibitor (ARNI) dosing should be adjusted to facilitate Beta-blocker titration.
4. ARNI's should be considered first line over ACE or ARB.
5. Titrare all meds to target doses if BP/HR allows on an every 2-4 week interval.
6. Regular monitoring of symptoms, blood pressure, heart rate, weight and BMP should guide dosage titrations and which medication to titrate at next contact.
7. Some patients only tolerate low doses of HFrEF medications and have worsening intolerance of HFrEF medications (based on the evaluation of home vitals) or end-organ dysfunction (elevated creatinine). Physicians should consider referral to cardiology to evaluate advanced heart failure therapies (LVAD and transplant consideration) in these patients.
### Table 1 Starting and Target Doses of Select GDMT and Novel Therapies for HF

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-Blockers: Must be one of these three for HFrEF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25 mg twice daily for weight &lt;85 kg and 50 mg twice daily for weight ≥85 kg</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5–25 mg daily</td>
<td>200 mg daily</td>
</tr>
<tr>
<td><strong>ARNIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>24/26 mg–49/51 mg twice daily</td>
<td>97/103 mg twice daily</td>
</tr>
<tr>
<td><strong>ACEIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg 3× daily</td>
<td>50 mg 3× daily</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice daily</td>
<td>10–20 mg twice daily</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–5 mg daily</td>
<td>20–40 mg daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4–8 mg daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>25–50 mg daily</td>
<td>150 mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 mg twice daily</td>
<td>160 mg twice daily</td>
</tr>
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</table>
Table 1 Starting and Target Doses of Select GDMT and Novel Therapies for HF

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Target Dose</th>
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</thead>
<tbody>
<tr>
<td><strong>Aldosterone antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg daily</td>
<td>50 mg daily</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5–25 mg daily</td>
<td>25–50 mg daily</td>
</tr>
<tr>
<td><strong>SGLT2 inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>10 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>25 mg 3× daily</td>
<td>75 mg 3× daily</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>20 mg 3× daily</td>
<td>40 mg 3× daily</td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td>20 mg/37.5 mg (1</td>
<td>2 tabs 3× daily</td>
</tr>
<tr>
<td>isosorbide dinitrate/hydr</td>
<td>tab) 3× daily</td>
<td></td>
</tr>
<tr>
<td><strong>Ivabradine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>2.5–5 mg twice daily</td>
<td>Titrate to heart rate 50–60 beats/min. Maximum dose 7.5 mg twice daily</td>
</tr>
</tbody>
</table>
Pharmacy Pearls for Prescribers

HFrEF Stage C Treatment

- ARNI/ACEI/ARB (ARNI preferred; Figures 3A and 3B), AND evidence-based beta-blocker (Figure 3C) with diuretic agent (Figure 3D) as needed

For patients with eGFR ≥ 30 mL/min/1.73 m² or creatinine ≤ 2.5 mg/dL in males or ≤ 2.0 mg/dL in females or K⁺ ≤ 5.0 mEq/L, NYHA class II-IV

Add Aldosterone antagonist (Figure 3E)

For patients meeting eGFR criteria (Figure 3F), NYHA class II-IV

Add SGLT2 inhibitor (Figure 3F)

For patients with persistent volume overload, NYHA class II-IV

Titrate Diuretic agent (Figure 3D)

For persistently symptomatic Black patients despite ARNI/beta-blocker/aldosterone antagonist/SGLT2 inhibitor, NYHA class III-IV

Add Hydralazine + isosorbide dinitrate (Figure 3G)

For patients with resting HR ≤ 70, on maximally tolerated beta-blocker dose in sinus rhythm, NYHA class II-III

Add Ivabradine (Figure 3H)

References:


*ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, please consult Figure 3 and text for guidance on initiation.

*Carvedilol, metoprolol succinate, or bisoprolol.

ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; K⁺ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

4. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee | Journal of the American College of Cardiology (jacc.org)
Helpful Pearls on Medication Titrations and Diuresis!

Executive Summary: The use of Guideline Directed Medical Therapy (GDMT) improves clinical outcomes in patients with heart failure. Despite this, many heart failure patients are difficult to achieve GDMT for different reasons. This document will hopefully help with next steps for the different situations that come up during medication titration for heart failure.

1. Congested
   a. Titrate angiotensin receptor neprilysin inhibitor (ARNI) or ACE/ARB at that titration schedule
   b. Beta blockers should not be started or increased when patients have congestion
   c. Increase loop diuretic dose, or add spironolactone if has not been started

2. Low blood pressures
   a. Consider switching to metoprolol succinate from carvedilol
   b. Add SGLT2 inhibitor
   c. Slow your titration, and only quit titrating if SBP drop <90 or patient becomes symptomatic

3. Beta Blocker equivalence
   a. Metoprolol: Carvedilol: Bisoprolol
      i. 25mg daily: 6.25mg bid: 1.25 mg daily

4. Increased potassium > 5
   a. Evaluate patients diet and start low potassium diet
   b. Decrease spironolactone
   c. Stop potassium supplements
   d. Recheck in one week
   e. If potassium ever increases to >5.4, stop spironolactone, but continue ARNI/ACE/ARB, repeat BMP in one week

5. High PVC burden (>10% on Zio patch)
   a. Recommend carvedilol for beta blocker
   b. BB should be titrated first
   c. Understand home pulse may be inaccurate if patient has significant amount of PVCs
      i. This means home pulse of 40s is not a reason to decrease BB. If worried about low pulse get ECG.

6. Cardiorenal syndrome
   a. Slow titrations of ARNI/ACE/ARB required
   b. Evaluate for congestion and increase loop if needed
   c. An increase in creatinine > 30% with medication titrations, consider consult to heart failure specialist (possible cardiomems candidate, or advance heart failure work up)

7. African American
   a. Consider adding hydralazine with isosorbide dinitrate along with ARNI/ACE/ARB if patient has blood pressure room
   b. Titrate slow with education that headache is likely for first week and with every dose increase
8. Follow up labs with titrations
   a. ARNI/ACEI/ARB = BMP 2 weeks after every dose increase
   b. Loop diuretic changes = BMP with in one week of change
   c. Spironolactone = BMP weekly x 2 weeks, then another BMP at 6 weeks
   d. Beta Blockers = no labs, vitals at 2 weeks
   e. SGLT2 = BMP periodically, will likely have BMP evaluation for other meds that are being titrated. Do not be concerned about a dip in GFR immediately after starting SGLT2

9. What to do with recovered ejection fraction patients?
   a. Do not stop HFrEF medications

Heart failure team diuretic protocol for heart failure patients with a weight gain of greater than 3 pounds in a day or greater than 5 pounds in a week

| Step A | Double daily oral loop diuretic dose or increase to maximum daily dose if doubled dose exceeds maximum. If already at maximum dose, then skip to Step B. (Max daily doses are: furosemide 320mg; bumetanide 10mg; torsemide 200 mg.)
|        | If weight the next day is decreased ≥ 2lbs, continue increased diuretic dose until goal weight is reached, then have patient resume usual dose of diuretic. Notify provider of outcome.
|        | If weight the next day is decreased by < 2 lbs, continue increased diuretic dose and continue to Step B.

| Step B | Add metolazone 2.5mg (if already on metolazone 2.5mg daily maintenance dose, give additional 2.5mg for 5mg total).
|        | If already taking 5mg of metolazone daily then skip to Step C.
|        | If weight the next day is decreased by ≥ 2 lbs, continue increased diuretic dose plus metolazone from step B until target weight is reached. When target weight is reached, have patient resume usual dose of diuretic. Notify the provider of outcome.
|        | If weight the next day is decreased by < 2lbs, discontinue all oral loop diuretics and continue to step C.

| Step C | Administer IV loop diuretic:
|        | Per Outpatient IV diuretic orders. Done at North Central Heart Clinic.
|        | Continue metolazone dose from Step B while administering the IV diuretic.

| Step D | If weight decreased by ≥ 2 lbs but not yet at target, continue IV medication per step C until target weight is reached. When the target weight is reached, adjust home diuretic dose to maintain euvoemla. If patient was previously on furosemide consider a change to torsemide or bumetanide.
|        | If target weight not reached with IV diuretics, consider admission.
|        | If after 24 hours with IV medication weight not decreased by ≥ 2lbs consider admission.

References:


Heart Failure Diuresis Pearls

**Executive Summary:** In general, the goal of long-term diuretic dosing is to use the lowest dose that permits effective maintenance of volume status. Optimization of Guideline-Directed Medical Therapy (GDMT) may allow reduction in loop diuretic dosing, and dose reduction may be required to mitigate the risk of hypotension or volume depletion.

There are numerous factors in heart failure patients that can impair GFR and reduce renal blood flow leading to different responses to diuretic therapy, even in patients with similar GFRs. Diuretic response is dependent on reaching a threshold and maintaining drug concentration above that threshold to maximize diuresis. This means if you **under** dose a diuretic you will have little to no effect, because you will not have reached threshold target doses. This is oftentimes seen in acute heart failure patients as the threshold increases as volume status increases.

**Diuretic pearls in heart failure**

1. Loop diuretics should be used first for congestion (starting doses listed below).
   a. Weights daily at home. Watching for weight gains >3 lbs in one day or 5 lbs in one week.
   b. BMP weekly or sooner while titrating diuretics.
      i. Replace potassium as needed (below is an outpatient potassium replacement that is used in NCH heart failure clinic for guidance on replacement)
2. Loop titration for patients with increased volume status who are already on diuretic.
   a. Escalation
      i. Double dose
      ii. Change to twice daily dosing
      iii. Triple dose
         1. Consider adding short term dosing of thiazide or thiazide like diuretic (Usually metolazone)
   b. Dose increases from 20mg to 40mg (furosemide) provides more diuresis than when a patient increases from 100 to 120 mg. Diuretic thresholds require larger loop doses as volume status increases to achieve similar diuresis. A patient on furosemide 100 mg will likely need 200 mg to achieve the same diuresis as a patient on 20 mg increasing to 40 mg.
3. Consider starting patients on torsemide vs. furosemide. Torsemide provides a more reliable diuretic response. For patients who are on furosemide and have demonstrated poor response, consider a change to torsemide or bumetanide. Torsemide or bumetanide have better oral bioavailability (80-100%). Furosemide oral bioavailability decreases significantly as volume status increases. Be on the watch for TRANSFORM-HF trial to be published this year comparing torsemide to furosemide for HF patients.
4. Creatinine increase alone does not mean you stop diuresis on a patient that is volume overloaded. Creatinine increases can also be caused by cardio-renal syndrome, and congestion can worsen kidney function during acute decompensated
heart failure. Patient’s volume status must be assessed before decreasing diuretics solely based on a creatinine jump. If cardio-renal syndrome is suspected referral to HF specialist and nephrology are warranted.

Suggested conversion:

<table>
<thead>
<tr>
<th>Furosemide doses comparison to torsemide and bumetanide doses.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Furosemide</strong></td>
</tr>
<tr>
<td>20 mg</td>
</tr>
<tr>
<td>40 mg</td>
</tr>
<tr>
<td>60 mg</td>
</tr>
<tr>
<td>80-100 mg</td>
</tr>
<tr>
<td><strong>Max dose:</strong> 320 mg</td>
</tr>
</tbody>
</table>

5. When to consider Metolazone?
   a. Chronic metolazone dosing should only be used after loop diuretics have been titrated up to max doses.
   b. For patients with severe congestion, a 2-3 day course of metolazone can be used with loop diuretic to speed up diuresis. Once euvolemia has been reached, discontinue metolazone, and maintain euvolemia with lowest possible loop diuretic dose.
   c. Metolazone increases risk of hypokalemia, hyponatremia, worsening renal function, and mortality when patients require chronic treatment.

6. When euvolemia is reached, addition of GDMT spironolactone or eplerenone with a reduction of loop diuretic to lowest possible dose would be indicated.

7. If hemodynamically stable, and unable to achieve diuresis with increased loop diuretic and metolazone could consider outpatient IV diuresis. Should consider referral to heart failure specialist.

**Potassium Replacement by Level of Kidney Function**

Please note, these doses are in addition to the patient’s baseline dose of potassium chloride.

<table>
<thead>
<tr>
<th>Creatinine &gt; 2 mg/dl</th>
<th>Creatinine ≤ 2 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>K ≤ 3.0 – notify provider</td>
<td>40 mEq BID</td>
</tr>
<tr>
<td>K 3.1-3.3</td>
<td>20 mEq BID</td>
</tr>
<tr>
<td>K 3.4-3.6</td>
<td>20 mEq daily</td>
</tr>
</tbody>
</table>
Table 1. Pharmacokinetic and Pharmacodynamic Properties of Common Loop Diuretics

<table>
<thead>
<tr>
<th></th>
<th>Furosemide</th>
<th>Bumetanide</th>
<th>Torsemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative IV potency, mg</td>
<td>40</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>PO to IV conversion, approximate</td>
<td>2:1</td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>10–100 (average = 50)</td>
<td>80–100</td>
<td>80–100</td>
</tr>
<tr>
<td>Initial outpatient PO dose, mg</td>
<td>20–40</td>
<td>0.5–1</td>
<td>5–10</td>
</tr>
<tr>
<td>Maintenance outpatient PO dose, mg</td>
<td>40–240</td>
<td>1–5</td>
<td>10–20</td>
</tr>
<tr>
<td>Maximum daily IV dose, mg*</td>
<td>600</td>
<td>10</td>
<td>200</td>
</tr>
</tbody>
</table>

Figure 2. Pharmacodynamics of Loop Diuretic Pharmacology
Loop diuretics have steep dose-response curves, meaning that there is little effect until a threshold is achieved, beyond which a ceiling of effect is reached. In patients with heart failure, the dose-response curve is shifted downward and to the right. Note that the x-axis for diuretic dose is on the log scale, suggesting that substantial increases in diuretic dosing are required to achieve an increase in diuretic effect. ADHF = acute decompensated heart failure.

References:


Huang X, Dorhout Mees E, Vos P, Hamza S, Braam B. Everything we always wanted to know about furosemide but were afraid to ask. Am J Physiol Renal Physiol 2016;310:F958–71. Everything we always wanted to know about furosemide but were afraid to ask | American Journal of Physiology-Renal Physiology


Outpatient IV Diuresis:

Executive Summary: Acute heart failure decompensation episodes often require hospitalizations. Given the economic and increasing emphasis on reduction of hospitalizations, it is important to look at ways we can prevent acute heart failure hospitalizations. Since the majority of hospitalizations for heart failure are a result of worsening congestion, and loop diuretics are the mainstay of therapy for 90% of heart failure hospitalizations, it only makes sense to add outpatient diuresis to the clinician’s tool belt.

Key questions

- **Who?**
  - Decompensated Heart Failure (reduced or preserved) with evidence of hypervolemia on exam
  - Hemodynamically stable

- **When?**
  - If titration of oral loop diuretics at home have not resulted in adequate diuresis and patient is still symptomatic
  - If the patient is having significant heart failure symptoms and needs aggressive therapy in the next 24hrs to prevent admission.

- **Where?**
  - Dedicated infusion center or adequately staffed physician office
    - Patients will require significant amount of staff time to prepare and administer infusion.
• Follow up?
  o BMP and symptom evaluation 24-48 hrs after infusion
  o Replace electrolytes as needed

<table>
<thead>
<tr>
<th>Potassium replacement</th>
<th>Creatinine &gt; 2 mg/dl</th>
<th>Creatinine ≤ 2 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>K ≤ 3.0 – notify provider</td>
<td>40 mEq BID</td>
<td>40 mEq TID (or 60 mEq BID)</td>
</tr>
<tr>
<td>K 3.1-3.3</td>
<td>20 mEq BID</td>
<td>20 mEq TID (or 40 mEq AM and 20 mEq PM)</td>
</tr>
<tr>
<td>K 3.4-3.6</td>
<td>20 mEq daily</td>
<td>20 mEq BID (or 40 mEq daily)</td>
</tr>
</tbody>
</table>

*Additional potassium added to current potassium supplementation. Follow BMP in one week.

  o If patient remains symptomatic can give additional outpatient IV diuretic dose
    - If patient requires more than 3 days of outpatient diuresis consider admission.

• Dosing (Most of dosing recommendations come from the Dose Trial)
  o Double the patients home loop diuretic dose given as IV furosemide equivalence.
  o Doses >100 mg must be given as an infusion. Doses < 100 mg can be given as a slow push not to exceed 20 mg/min.
  o Consider giving patient a urinal or hat if they require a long drive home after infusion.

References:

