Heart Failure Medication Titration Protocol

Titration Parameters

Blood Pressure Parameters

- **Titration range:** <200/110 and >80/40 mmHg
- **Goal range:** <120/80 and >90/50 mmHg

Heart Rate Parameters

- **Titration minimum:** ≥50 beats per minuteIf only 2 of 20 events were attacks, then predicting no attack every time would achieve 90% accuracy but 0% recall. The total failure to detect threats would be masked.
-
- Accuracy would simply rise because the benign events dominate. Precision and recall would fall because of the lack of positive examples.
-
- And this demonstrates why accuracy can be misleading if the data is imbalanced, it measures overall correctness instead of success in detecting certain events and outcomes.
-
- **Goal range:** <90 and >55 beats per minute

Titration Strategy

Select ONE approach:

Option A: Single Drug Titration

- Titrate one medication to target dose before adding or titrating the next medication
- Allows clear assessment of individual drug effects and side effects
- May take longer to achieve optimal therapy

Option B: Multiple Drug Titration

Sub-option 1: Optimization by order of drugs

- Initiate multiple drugs at low doses simultaneously

- Titrate Drug 1 to target → then Drug 2 to target → then Drug 3 to target, etc.
- Faster achievement of guideline-directed medical therapy (GDMT)

Sub-option 2: Alternating optimization

- Initiate multiple drugs at low doses simultaneously
- Alternate titrations: Drug 1 → Drug 2 → Drug 1 → Drug 3 → Drug 2, etc.
- Distributes side effects and improves overall tolerability

Medication Classes and Dosing

1. ACE Inhibitors (ACE-I)

Enalapril:

- Starting dose: 2.5 mg PO twice daily
- Incremental doses: 2.5 mg → 5 mg → 10 mg → 20 mg PO twice daily
- **Maximum dose: 20 mg PO twice daily**

Lisinopril:

- Starting dose: 2.5-5 mg PO daily
- Incremental doses: 2.5 mg → 5 mg → 10 mg → 20 mg → 40 mg PO daily
- **Maximum dose: 40 mg PO daily**

Ramipril:

- Starting dose: 1.25-2.5 mg PO daily
- Incremental doses: 1.25 mg → 2.5 mg → 5 mg → 10 mg PO daily
- **Maximum dose: 10 mg PO daily**

Captopril:

- Starting dose: 6.25 mg PO three times daily
- Incremental doses: 6.25 mg → 12.5 mg → 25 mg → 50 mg PO three times daily
- **Maximum dose: 50 mg PO three times daily**

Contraindications:

- History of angioedema with ACE-I
- Bilateral renal artery stenosis
- Pregnancy
- Concomitant use with aliskiren in patients with diabetes
- Concurrent or recent (<48 hours) use of neprilysin inhibitor

Hold or Discontinue if:

- **Potassium >5.5 mEq/L** (hold; may resume at lower dose if K+ normalizes)
- **Creatinine increase >30% from baseline** (hold; reassess in 1-2 weeks)
- **eGFR <20-30 mL/min** (use caution; consider dose reduction or discontinuation)
- **Symptomatic hypotension** with SBP <80-90 mmHg
- **Angioedema** (discontinue permanently)
- **Hyperkalemia persisting >6.0 mEq/L** despite intervention (discontinue)

---

2. Angiotensin Receptor Blockers (ARBs)

Losartan:

- Starting dose: 25 mg PO daily
- Incremental doses: 25 mg → 50 mg → 100 mg PO daily
- **Maximum dose: 100 mg PO daily** (or 50 mg twice daily)

Valsartan:

- Starting dose: 40 mg PO twice daily
- Incremental doses: 40 mg → 80 mg → 160 mg PO twice daily
- **Maximum dose: 160 mg PO twice daily**

Candesartan:

- Starting dose: 4-8 mg PO daily
- Incremental doses: 4 mg → 8 mg → 16 mg → 32 mg PO daily
- **Maximum dose: 32 mg PO daily**

Contraindications:

- History of angioedema with ARB
- Bilateral renal artery stenosis
- Pregnancy
- Concomitant use with aliskiren in patients with diabetes
- Concurrent or recent (<48 hours) use of neprilysin inhibitor

Hold or Discontinue if:

- **Potassium >5.5 mEq/L** (hold; may resume at lower dose if K+ normalizes)
- **Creatinine increase >30% from baseline** (hold; reassess in 1-2 weeks)
- **eGFR <20-30 mL/min** (use caution; consider dose reduction or discontinuation)
- **Symptomatic hypotension** with SBP <80-90 mmHg
- **Angioedema** (discontinue permanently)

- **Hyperkalemia persisting >6.0 mEq/L** despite intervention (discontinue)

---

3. Neprilysin Inhibitor/ARB (ARNI)

Sacubitril/Valsartan (Entresto):

Important: Initiate 48 hours following cessation of previous ACE-I

Starting dose:

- **24/26 mg PO twice daily** if:
    - Patient not currently taking ACE-I/ARB, OR
    - Currently taking ACE-I/ARB equivalent to ≤10 mg Enalapril daily, OR
    - eGFR <30 mL/min, OR
    - Hepatic impairment Child-Pugh Class B
- **49/51 mg PO twice daily** if:
    - Currently taking ACE-I/ARB equivalent to >10 mg Enalapril daily

Incremental doses: 24/26 mg → 49/51 mg → 97/103 mg PO twice daily

Maximum dose: 97/103 mg PO twice daily

Contraindications:

- History of angioedema with ACE-I, ARB, or neprilysin inhibitor
- Concurrent use with ACE-I (must wait 48 hours after last ACE-I dose)
- Pregnancy
- Severe hepatic impairment (Child-Pugh Class C)

Hold or Discontinue if:

- **Potassium >5.5 mEq/L** (hold; may resume at lower dose if K+ normalizes)
- **Creatinine increase >30% from baseline** (hold; reassess in 1-2 weeks)
- **eGFR <20 mL/min** (use with extreme caution or consider discontinuation)
- **Symptomatic hypotension** with SBP <80-90 mmHg
- **Angioedema** (discontinue permanently)
- **Hyperkalemia persisting >6.0 mEq/L** despite intervention (discontinue)

---

4. Aldosterone Antagonists

Spironolactone:

- Starting dose: 12.5 mg PO daily
- Incremental doses: 12.5 mg → 25 mg → 50 mg PO daily
- **Maximum dose: 50 mg PO daily** (25 mg daily often sufficient)

Eplerenone:

- Starting dose: 25 mg PO daily
- Incremental doses: 25 mg → 50 mg PO daily
- **Maximum dose: 50 mg PO daily**

Contraindications:

- **Baseline potassium >5.0 mEq/L**
- **eGFR <30 mL/min**
- Concurrent use of strong CYP3A4 inhibitors (eplerenone)
- Addison's disease or hyperkalemia

Hold or Discontinue if:

- **Potassium >5.5 mEq/L** (hold; may resume at lower dose if K+ 4.5-5.0 mEq/L)
- **Potassium >6.0 mEq/L** (discontinue)
- **Creatinine increase >30% from baseline or eGFR drops to <30 mL/min** (hold or discontinue)
- **Severe gynecomastia or breast tenderness** (consider switching spironolactone to eplerenone)
- **Symptomatic hypotension**

---

5. Beta Blockers

Carvedilol:

- Starting dose: 3.125 mg PO twice daily
- Incremental doses: 3.125 mg → 6.25 mg → 12.5 mg → 25 mg PO twice daily
- **Maximum dose: 25 mg PO twice daily** (50 mg twice daily if weight >85 kg)

Metoprolol Succinate (Extended-Release):

- Starting dose: 12.5-25 mg PO daily
- Incremental doses: 12.5 mg → 25 mg → 50 mg → 100 mg → 200 mg PO daily
- **Maximum dose: 200 mg PO daily**

Bisoprolol:

- Starting dose: 1.25 mg PO daily
- Incremental doses: 1.25 mg → 2.5 mg → 5 mg → 10 mg PO daily
- **Maximum dose: 10 mg PO daily**

Contraindications:

- Symptomatic bradycardia or heart rate <50 bpm
- Second or third-degree AV block (without pacemaker)
- Sick sinus syndrome (without pacemaker)
- Severe decompensated heart failure requiring inotropic support
- Severe asthma or active bronchospasm
- Cardiogenic shock

Hold or Discontinue if:

- **Heart rate <50 bpm** (hold or reduce dose)
- **Heart rate <45 bpm** (hold; consider discontinuation if persistent)
- **Symptomatic bradycardia** (reduce dose or discontinue)
- **Second or third-degree AV block** develops (discontinue)
- **SBP <80-85 mmHg with symptoms** (hold or reduce dose)
- **Acute decompensated heart failure** requiring IV diuretics/inotropes (hold temporarily)
- **Severe bronchospasm** (discontinue)

---

6. Hydralazine/Isosorbide Dinitrate

Hydralazine:

- Starting dose: 25 mg PO three times daily
- Incremental doses: 25 mg → 37.5 mg → 50 mg → 75 mg PO three times daily
- **Maximum dose: 75 mg PO three times daily** (up to 100 mg TID in some protocols)

Isosorbide Dinitrate:

- Starting dose: 20 mg PO three times daily
- Incremental doses: 20 mg → 30 mg → 40 mg PO three times daily
- **Maximum dose: 40 mg PO three times daily**

Fixed-Dose Combination (BiDil):

- Each tablet contains: Hydralazine 37.5 mg + Isosorbide dinitrate 20 mg
- Starting dose: 1 tablet PO three times daily
- Incremental doses: 1 tablet → 2 tablets PO three times daily
- **Maximum dose: 2 tablets PO three times daily**

Contraindications:

- Severe hypotension
- Concurrent use of PDE-5 inhibitors (sildenafil, tadalafil) with nitrates
- Recent MI (within 24-48 hours) for nitrates
- Drug-induced lupus syndrome

Hold or Discontinue if:

- **SBP <85-90 mmHg with symptoms** (hold or reduce dose)
- **Symptomatic hypotension or orthostasis**
- **Drug-induced lupus syndrome** develops (discontinue hydralazine; positive ANA, arthralgias, fever)
- **Severe headache intolerant to treatment** (reduce nitrate dose or discontinue)
- **Severe tachycardia** (HR >110-120 bpm) - consider adding beta blocker or reducing dose

---

7. SGLT-2 Inhibitors

Dapagliflozin:

- Starting dose: 10 mg PO daily
- **Maximum dose: 10 mg PO daily** (no titration required)

Empagliflozin:

- Starting dose: 10 mg PO daily
- **Maximum dose: 10 mg PO daily** (no titration required)

Sotagliflozin:

- Starting dose: 200 mg PO daily (if eGFR ≥25 mL/min)
- Incremental doses: 200 mg → 400 mg PO daily
- **Maximum dose: 400 mg PO daily**

Contraindications:

- **eGFR <20 mL/min** (dapagliflozin, empagliflozin)
- **eGFR <25 mL/min** (sotagliflozin)
- Type 1 diabetes (relative contraindication)
- History of diabetic ketoacidosis
- Dialysis

Hold or Discontinue if:

- **eGFR falls to <20 mL/min** (discontinue dapagliflozin/empagliflozin)
- **eGFR falls to <25 mL/min** (discontinue sotagliflozin)
- **Diabetic ketoacidosis** (DKA) or euglycemic DKA develops (discontinue permanently)
- **Severe dehydration or volume depletion**
- **Recurrent urinary tract infections or genital mycotic infections** (consider discontinuation)
- **Fournier's gangrene** (necrotizing fasciitis of perineum) - discontinue immediately
- **Acute kidney injury** (hold temporarily)

---

8. Soluble Guanylate Cyclase (sGC) Stimulator

Vericiguat:

- Starting dose: 2.5 mg PO daily
- Incremental doses: 2.5 mg → 5 mg → 10 mg PO daily (double dose every 2 weeks)
- **Maximum dose: 10 mg PO daily**

Contraindications:

- Concomitant use with PDE-5 inhibitors (riociguat, sildenafil, tadalafil)
- Pregnancy
- Severe hepatic impairment (Child-Pugh Class C)

Hold or Discontinue if:

- **SBP <90 mmHg with symptoms** (hold or reduce dose)
- **Symptomatic hypotension**
- **Concurrent need for PDE-5 inhibitor** (discontinue one or the other)
- **Pregnancy** (discontinue immediately)
- **Worsening anemia** (monitor hemoglobin; may reduce dose or discontinue if clinically significant)

Laboratory Monitoring

Labs to Monitor:

- **Basic Metabolic Panel (BMP):** Sodium, potassium, chloride, bicarbonate, glucose
- **Renal function:** Creatinine, BUN, eGFR
- **Additional:** Magnesium (if on loop diuretics), Hemoglobin/Hematocrit (baseline and with SGLT-2i or vericiguat)

Monitoring Schedule:

Baseline: Before initiation of any medication

After initiation or dose change (the ordering physician can specify this):

- **1-2 weeks** for:
    - Aldosterone antagonists (check BMP, especially K+ and creatinine)
    - ACE-I/ARB/ARNI (check BMP, creatinine, eGFR)
    - Any combination changes with ACE-I/ARB/ARNI + aldosterone antagonist
- **2-4 weeks** for:
    - Beta blockers (if renal or electrolyte concerns present)
    - SGLT-2 inhibitors (check BMP, creatinine, eGFR)
    - sGC stimulator (check BMP, hemoglobin)
    - Hydralazine/nitrates (generally less frequent labs needed unless concerns)

Ongoing monitoring:

- **As needed** on maintenance doses
- **More frequently** if baseline abnormalities or during acute illness

General Hold or Adjust Criteria Across Multiple Drug Classes:

- **Potassium >5.5 mEq/L:** Hold aldosterone antagonist; consider dose reduction of ACE-I/ARB/ARNI
- **Potassium >6.0 mEq/L:** Discontinue aldosterone antagonist; reduce or hold ACE-I/ARB/ARNI
- **Creatinine increase >30% from baseline:** Hold ACE-I/ARB/ARNI; reassess in 1-2 weeks
- **eGFR <20-30 mL/min:** Consider discontinuing SGLT-2 inhibitor, dose reduction or discontinuation of ACE-I/ARB/ARNI
- **Sodium <130 mEq/L:** Evaluate volume status; adjust diuretics; monitor closely
- **Symptomatic hypotension:** Hold or reduce offending agents (ACE-I/ARB/ARNI, hydralazine/nitrates, beta blockers)

Titration Sequences (Examples)

SINGLE DRUG APPROACH:

Example Sequence:

1. **Start beta blocker** at low dose → titrate to target over 6-8 weeks

2. **Start ACE-I/ARB/ARNI** at low dose → titrate to target over 4-6 weeks (check labs at 1-2 weeks after each change)
3. **Start aldosterone antagonist** at low dose → titrate to target over 2-4 weeks (check labs at 1 week after each change)
4. **Add SGLT-2 inhibitor** at standard dose (check labs at 2-4 weeks)
5. **Add sGC stimulator or hydralazine/nitrates** if indicated → titrate to target

Timeline: 4-6 months to reach full GDMT

MULTIPLE DRUG APPROACH - BY ORDER:

Example Sequence:

1. **Week 0:** Start beta blocker + ACE-I/ARB/ARNI (both at low doses); baseline labs
2. **Week 2:** Check labs (BMP, creatinine); Titrate beta blocker (check BP/HR)
3. **Week 4:** Titrate beta blocker (check BP/HR)
4. **Week 6:** Titrate beta blocker to target (check BP/HR)
5. **Week 8:** Check labs; Titrate ACE-I/ARB/ARNI (check BP)
6. **Week 10:** Check labs; Titrate ACE-I/ARB/ARNI (check BP)
7. **Week 12:** Check labs; Titrate ACE-I/ARB/ARNI to target (check BP)
8. **Week 14:** Add aldosterone antagonist; check labs at 1 week
9. **Week 16:** Check labs; Titrate aldosterone antagonist to target if appropriate
10. **Week 18:** Add SGLT-2 inhibitor + sGC stimulator if indicated; check labs at 2-4 weeks

Timeline: 3-4 months to reach full GDMT

MULTIPLE DRUG APPROACH - ALTERNATING:

Example Sequence:

1. **Week 0:** Start beta blocker + ACE-I/ARB/ARNI (both at low doses); baseline labs
2. **Week 2:** Check labs (BMP, creatinine); Titrate beta blocker (check BP/HR)
3. **Week 4:** Check labs; Titrate ACE-I/ARB/ARNI (check BP)
4. **Week 6:** Titrate beta blocker (check BP/HR)
5. **Week 8:** Check labs; Add aldosterone antagonist
6. **Week 9:** Check labs (1 week after aldosterone antagonist)
7. **Week 10:** Titrate ACE-I/ARB/ARNI (check labs, BP)
8. **Week 12:** Titrate beta blocker to target (check BP/HR)
9. **Week 14:** Check labs; Titrate aldosterone antagonist if appropriate
10. **Week 16:** Check labs; Titrate ACE-I/ARB/ARNI to target (check BP)
11. **Week 18:** Add SGLT-2 inhibitor + sGC stimulator if indicated; check labs at 2-4 weeks

Timeline: 3-4 months to reach full GDMT

Note: All sequences should be individualized based on patient hemodynamics, symptoms, lab values, and tolerability. Allow flexibility to slow titration or hold medications as clinically indicated. More frequent lab monitoring may be necessary in patients with baseline renal impairment, electrolyte abnormalities, or other comorbidities.

HF Med Titration Program Endpoint Definitions

Complete Success
The patient demonstrates consistent progress throughout the titration program, tolerating medication increases well and achieving all target therapeutic doses. The conversation concludes with the patient graduating from the program, having reached optimal medical therapy for their heart failure condition.

Partial Success
The patient shows variable responses to medication adjustments, with some drugs reaching their intended targets while others plateau at submaximal doses due to tolerance limitations or mild side effects. The conversation ends with program graduation at the maximum doses the patient can safely tolerate, which may be below ideal targets but represents meaningful therapeutic improvement.

Non-Adherence Failure
The patient exhibits a progressive pattern of missed doses and declining medication-taking behavior. Repeated adherence issues prevent safe titration advancement, and the conversation terminates with discontinuation from the remote monitoring program due to inability to maintain the medication regimen.

Side Effect Failure
The patient experiences increasingly problematic adverse effects from medications that raise safety concerns despite dose adjustments or management attempts. The conversation concludes with early program termination as continuing therapy poses unacceptable risks to patient wellbeing.

Acute Decompensation with ED Referral
During the conversation, the patient reports acute worsening heart failure symptoms requiring immediate medical evaluation. The agent directs the patient to the emergency department and provides explicit safety instructions to seek immediate care if symptoms deteriorate further while awaiting physician callback. The program pauses pending urgent medical assessment.

Hospitalization Pause
The patient experiences significant clinical deterioration requiring hospital admission. The

conversation ends with temporary suspension of the titration program, with plans to reassess the patient's eligibility and restart protocol after hospital discharge and stabilization.

Patient Withdrawal
The patient expresses unwillingness or refusal to continue with the medication titration process, despite clinical appropriateness. The conversation concludes with voluntary withdrawal from the program at the patient's request, reflecting their preference to discontinue remote monitoring.