

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. Titrate 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.

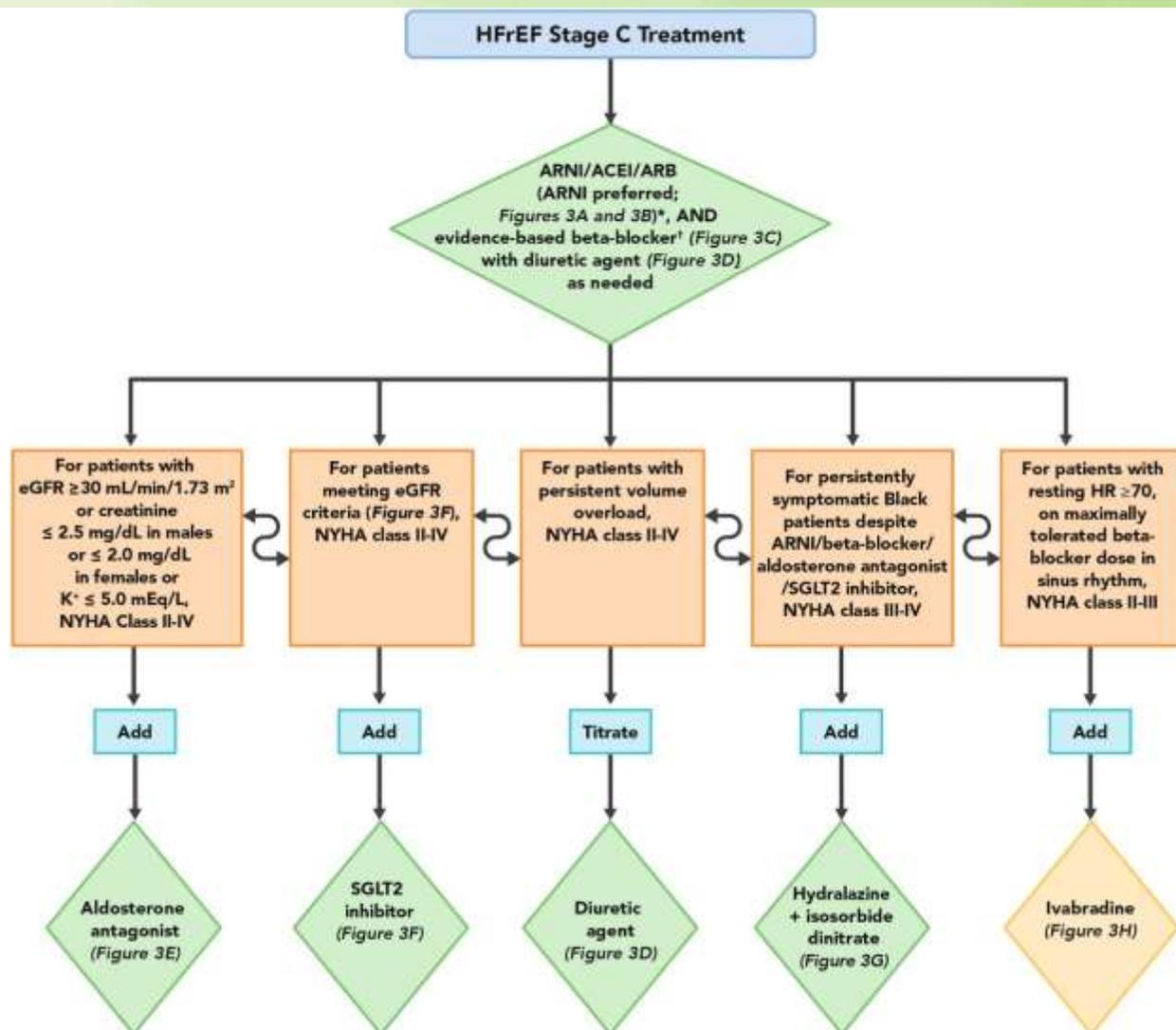
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Table 1 Starting and Target Doses of Select GDMT and Novel Therapies for HF		
	Starting Dose	Target Dose
Beta-Blockers: Must be one of these three for HFrEF		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice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

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Table 1 Starting and Target Doses of Select GDMT and Novel Therapies for HF		
	Starting Dose	Target Dose
Aldosterone antagonists		
Eplerenone	25 mg daily	50 mg daily
Spirolactone	12.5–25 mg daily	25–50 mg daily
SGLT2 inhibitors		
Dapaqliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 mg daily
Vasodilators		
Hydralazine	25 mg 3x daily	75 mg 3x daily
Isosorbide dinitrate	20 mg 3x daily	40 mg 3x daily
Fixed-dose combination isosorbide dinitrate/hydralazine [±]	20 mg/37.5 mg (1 tab) 3x daily	2 tabs 3x daily
Ivabradine		
Ivabradine	2.5–5 mg twice daily	Titrate to heart rate 50–60 beats/min. Maximum dose 7.5 mg twice daily

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*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.

References:

1. Maddox TM, Januzzi JL Jr, Allen LA, et al. 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. *J Am Coll Cardiol* 2021;Jan 11.
2. Yancy CW, Januzzi JL, Allen LA, et al. 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 Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2018;71(2):201-230.

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3. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol.* 2017;70(6):776-803.
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 \(jacc.org\)](#)
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 Thomas M. Maddox, MD, MSc, FACC Chair James L. Januzzi, Jr., MD, FACC Vice Chair Larry A. Allen, MD, MHS, FACC Khadijah Breathett, MD, MS, FACC Javed Butler, MD, MBA, MPH, FACC Leslie L. Davis, PhD, RN, ANP-BC, FACC Gregg C. Fonarow, MD, FACC Nasrien E. Ibrahim, MD, FACC JoAnn Lindenfeld, MD, FACC Frederick A. Masoudi, MD, MSPH, FACC Shweta R. Motiwala, MD, MPH Estefania Oliveros, MD, MSc J. Herbert Patterson, PharmD Mary Norine Walsh, MD, MACC Alan Wasserman, MD, FACC Clyde W. Yancy, MD, MSc, MACC Quentin R. Youmans, MD

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 cardiomegaly 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

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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 HFReEF 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Administer IV loop diuretic: <ul style="list-style-type: none"> ◦ Per Outpatient IV diuretic orders. Done at North Central Heart Clinic. • Continue metolazone dose from Step B while administering the IV diuretic.
Step D	<ul style="list-style-type: none"> • 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 euvolemia. 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:

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Barsuk JH, Gordon RA, Cohen ER, et al. A diuretic protocol increases volume removal and reduces readmissions among hospitalized patients with acute decompensated heart failure. *Congest Heart Fail* 2013;19:53–60.

Felker M.G., Ellison D.H, Mullens W. et al., Diuretic Therapy for Patients with Heart Failure: JACC State-of-the-Art Review. *J AM Coll Cardiology*. 2020 Mar, 75 (10) 1178-1195. [Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review | Journal of the American College of Cardiology](#)

Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;364:797–805. [Diuretic Strategies in Patients with Acute Decompensated Heart Failure | NEJM](#)

Mullens W, Damman K, Harjola VP, et al. The use of diuretics in heart failure with congestion: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;21:137–55. [The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology - Mullens - 2019 - European Journal of Heart Failure - Wiley Online Library](#)

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

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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:

Furosemide doses comparison to torsemide and bumetanide doses.		
Furosemide	Torsemide	Bumetanide
20 mg	10 mg	0.5 mg
40 mg	20 mg	1 mg
60 mg	30 mg	1.5 mg
80-100 mg	40 mg	2 mg
Max dose: 320 mg	200 mg	10 mg

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.

	Creatinine > 2 mg/dl	Creatinine ≤ 2 mg/dl
K ≤ 3.0 – notify provider	40 mEq BID	40 mEq TID (or 60 mEq BID)
K 3.1-3.3	20 mEq BID	20 mEq TID (or 40 mEq AM and 20 mEq PM)
K 3.4-3.6	20 mEq daily	20 mEq BID (or 40 mEq daily)

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Table 1. Pharmacokinetic and Pharmacodynamic Properties of Common Loop Diuretics

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

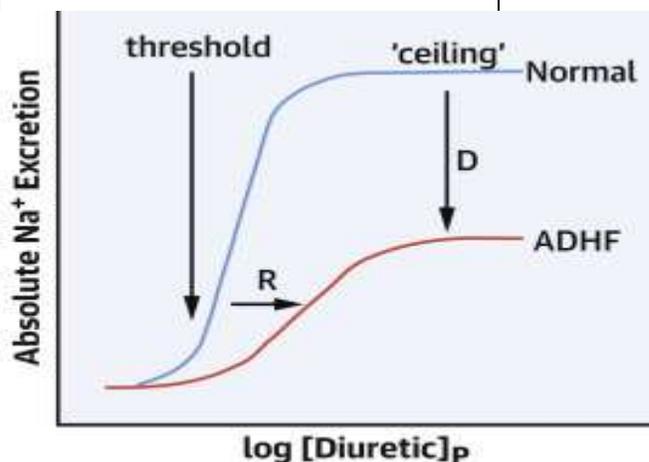


Figure 2. Pharmacodynamics of Loop Diuretic Pharmacology

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:

Felker M.G., Ellison D.H, Mullens W. et al., Diuretic Therapy for Patients with Heart Failure: JACC State-of-the-Art Review. J AM Coll Cardiology. 2020 Mar, 75 (10) 1178-1195. [Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review | Journal of the American College of Cardiology](#)

Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805. [Diuretic Strategies in Patients with Acute Decompensated Heart Failure | NEJM](#)

Mullens W, Damman K, Harjola VP, et al. The use of diuretics in heart failure with congestion: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21:137–55. [The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology - Mullens - 2019 - European Journal of Heart Failure - Wiley Online Library](#)

Pharmacy Pearls for Prescribers

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](#)

Bishoy A., Michael M., Mina S., Meta-Analysis Comparing Torsemide Versus Furosemide in Patients With Heart Failure. *J Cardiol* 2020;125:92–99)

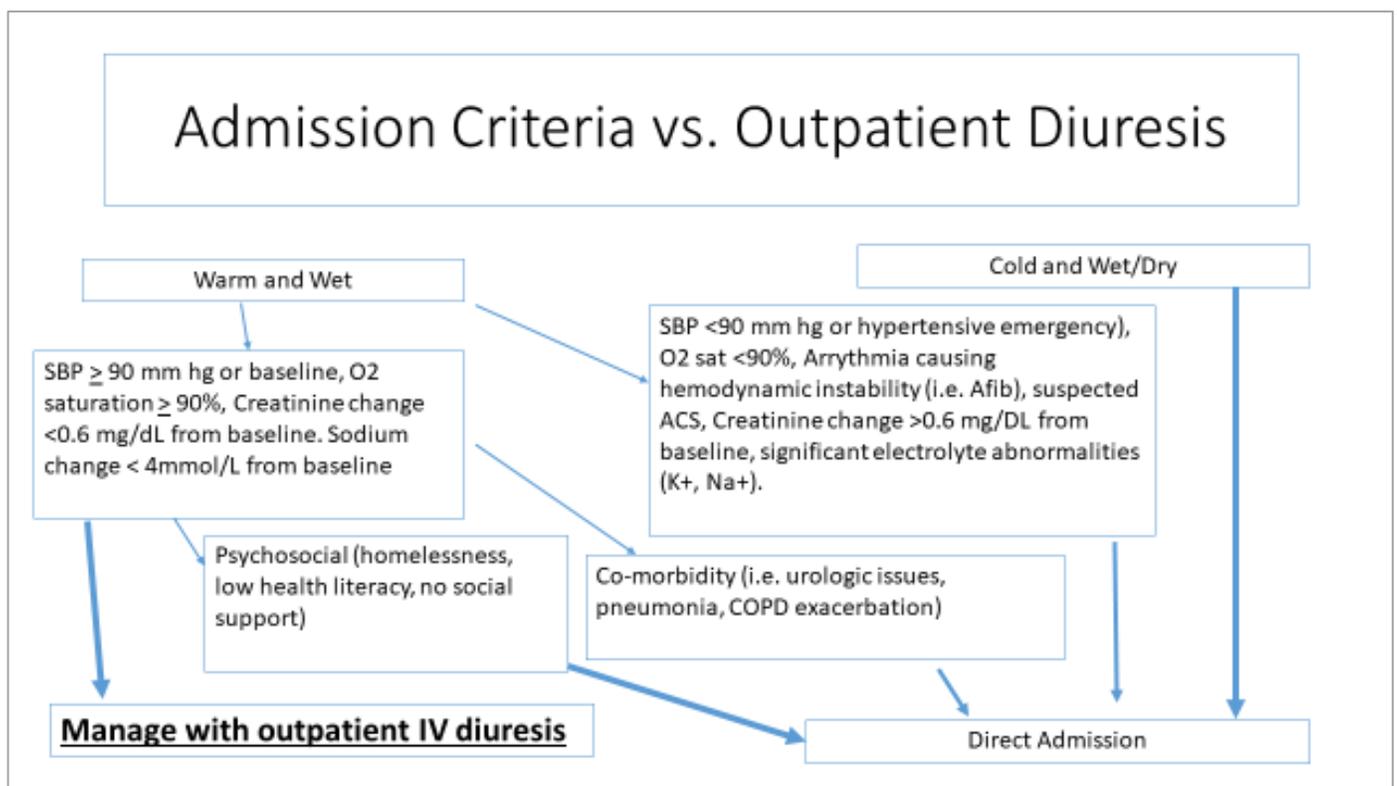
Müller K, Gamba G, Jaquet F, Hess B. Torasemide vs. furosemide in primary care patients with chronic heart failure NYHA II to IV—efficacy and quality of life. *Eur J Heart Fail* 2003;5:793–801.

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.

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- Follow up?
 - BMP and symptom evaluation 24-48 hrs after infusion
 - Replace electrolytes as needed

*Potassium replacement	Creatinine > 2 mg/dl	Creatinine ≤ 2 mg/dl
K ≤ 3.0 – notify provider	40 mEq BID	40 mEq TID (or 60 mEq BID)
K 3.1-3.3	20 mEq BID	20 mEq TID (or 40 mEq AM and 20 mEq PM)
K 3.4-3.6	20 mEq daily	20 mEq BID (or 40 mEq daily)

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

- 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)
 - Double the patients home loop diuretic dose given as IV furosemide equivalence.
 - 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.
 - Consider giving patient a urinal or hat if they require a long drive home after infusion.

References:

Buckley LF, Carter DM, Matta L, Cheng JW, Stevens C, Belenkiy RM, Burpee LJ, Young MA, Weiffenbach CS, Smallwood JA, Stevenson LW, Desai AS. Intravenous Diuretic Therapy for the Management of Heart Failure and Volume Overload in a Multidisciplinary Outpatient Unit. *JACC Heart Fail.* 2016 Jan;4(1):1-8. doi: 10.1016/j.jchf.2015.06.017. Epub 2015 Dec 2.

Felker M.G., Ellison D.H, Mullens W. et al., Diuretic Therapy for Patients with Heart Failure: JACC State-of-the-Art Review. *J AM Coll Cardiology.* 2020 Mar, 75 (10) 1178-1195. [Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review | Journal of the American College of Cardiology](#)

Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;364:797–805. [Diuretic Strategies in Patients with Acute Decompensated Heart Failure | NEJM](#)