The Medical Letter®
on Drugs and Therapeutics

Comparison Chart: Some Drugs for Heart Failure with Reduced Ejection Fraction (HFrEF)

Updated June 1, 2021

SUMMARY: TREATMENT OF HFrEF[1-3]

- Among patients with chronic heart failure, those with a left ventricular ejection fraction (LVEF) ≤40% are considered to have heart failure with reduced ejection fraction (HFrEF).
- An angiotensin receptor-neprilysin inhibitor (ARNI) is now preferred over an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for patients with NYHA class II-IV heart failure. The benefits are most evident in those with HFrEF. In patients who are unable to tolerate an ARNI or cannot access an ARNI due to cost, an ACE inhibitor or ARB should be used instead.
- In addition to an ARNI, ACE inhibitor or ARB, all patients with ACC/AHA Stage C HFrEF should take, unless contraindicated, an evidence-based beta blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter 2 (SGLT2) inhibitor.
- In patients who are volume overloaded, a diuretic should be added. Loop diuretics are more effective than thiazide diuretics in patients with heart failure.
- Black patients with HFrEF, especially those with persistent NYHA class III-IV symptoms despite use of target or maximally tolerated doses of an ARNI, ACE inhibitor, or ARB, a beta blocker, and an MRA, can benefit from addition of isosorbide dinitrate and hydralazine.
- In patients with NYHA class II-III heart failure and a LVEF ≤35% who are in sinus rhythm with a resting heart rate ≥70 bpm despite use of target or maximally tolerated doses of a beta blocker, addition of the I_f channel inhibitor ivabradine should be considered.
- In patients with symptomatic heart failure and a LVEF <45% who were recently hospitalized or required treatment with an IV diuretic, addition of the soluble guanylate cyclase (sGC) stimulator vericiguat modestly reduced the composite risk of first hospitalization for heart failure or cardiovascular death, but not the risk for cardiovascular death alone.
- Digoxin can decrease symptoms and the rate of hospitalization for heart failure in patients with HFrEF, but it does not reduce mortality. Data on the benefits of digoxin in the setting of contemporary heart failure treatments are lacking.

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- An ARNI is now preferred over an ACE inhibitor or ARB for patients with NYHA class II-IV heart failure. The benefits are most evident in those with HFrEF. In patients who are unable to tolerate an ARNI or cannot access an ARNI due to cost, an ACE inhibitor or ARB should be used instead.
- All patients with ACC/AHA Stage C (structural heart disease with prior or current heart failure symptoms) HFrEF should take, unless contraindicated, an ARNI (preferred), ACE inhibitor, or ARB, an evidence-based beta blocker, a MRA, and a SGLT2 inhibitor, and if volume overloaded, a diuretic.[1-3]

ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI)

DRUG	SOME ORAL FORMULATIONS	USUAL INITIAL ADULT DOSAGE	USUAL MAXIMUM ADULT DOSAGE	COST[4]	ADMINISTRATION/COMMENTS
Sacubitril/valsartan – *Entresto* (Novartis)	24/26, 49/51, 97/103 mg tabs	49/51 mg bid **Renal impairment:** eGFR <30mL/min/1.73 m^2: 24/26 mg bid **Hepatic impairment:** Moderate (Child-Pugh B): 24/26 mg bid Severe (Child-Pugh C): not recommended In those currently taking a low-dose ACE inhibitor or ARB (≤10 mg daily of enalapril or ≤160 mg daily of valsartan) or with *de novo* therapy, or in those with hypotension: 24/26 mg bid	97/103 mg bid	$582.90	▪ FDA-approved in 2015 to reduce the risk of hospitalization for heart failure and cardiovascular death in patients with NYHA class II-IV HFrEF (LVEF <40%)[5]; the indication has been expanded to include patients with chronic heart failure with any LVEF; the label specifies that benefits are most clearly evident in patients with an LVEF below normal ▪ Inhibition of neprilysin, which degrades several vasoactive peptides, enhances vasodilation and sodium excretion ▪ Dose should be doubled every 2 weeks as tolerated to a target of 97/103 mg twice daily ▪ Blood pressure, renal function, and electrolytes (serum potassium) should be monitored after initiation and during titration

ADVERSE EFFECTS

- Hypotension, renal impairment, and hyperkalemia can occur
- Neprilysin inhibition can cause angioedema; avoid use in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy and in those with hereditary angioedema

DRUG INTERACTIONS

- Contraindicated for use with or within 36 hours after the last dose of an ACE inhibitor because of the increased risk of angioedema
- Should not be used with an ARB
- Use with potassium-sparing diuretics, renin inhibitors, trimethoprim/sulfamethoxazole, or other drugs that increase serum potassium levels increases the risk of hyperkalemia
- Worsening of renal function and acute renal failure could occur in patients taking NSAIDs concurrently
- ARBs can increase lithium serum concentrations; frequent monitoring is recommended
- Valsartan is a substrate of OATP1B1; concomitant use with drugs that inhibit OATP1B1, such as atorvastatin, could increase valsartan serum concentrations[6]

PREGNANCY and LACTATION

- Contraindicated for use during pregnancy because of an increased risk of fetal renal failure and death
- No data on presence in breast milk

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

- An ARNI is now preferred over an ACE inhibitor or ARB for patients with NYHA class II-IV heart failure. The benefits are most evident in those with HFrEF. In patients who are unable to tolerate an ARNI or cannot access an ARNI due to cost, an ACE inhibitor or ARB should be used instead.
- All patients with ACC/AHA Stage C (structural heart disease with prior or current heart failure symptoms) HFrEF should take, unless contraindicated, an ARNI (preferred), ACE inhibitor, or ARB, an evidence-based beta blocker, a MRA, and a SGLT2 inhibitor, and if volume overloaded, a diuretic.[1-3]

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

DRUG	SOME ORAL FORMULATIONS	USUAL INITIAL ADULT DOSAGE	USUAL MAXIMUM ADULT DOSAGE	COST[4]	ADMINISTRATION/COMMENTS
Captopril – generic	12, 25, 50, 100 mg scored tabs	6.25 mg tid **Renal impairment:** CrCl 10-50 mL/min: 75% of normal dose q12-18h; CrCl <10 mL/min: 50% of normal dose q24h	50 mg tid	$160.40	▪ Improve symptoms (generally over 4-12 weeks), decrease the incidence of hospitalization for heart failure, and prolong survival in patients with HFrEF ▪ No data are available showing that one ACE inhibitor is more effective than any other for treatment of HFrEF ▪ Should be started at low doses and titrated up to the highest tolerated dose, targeting the usual maximum daily dosages ▪ Monitor blood pressure, renal function, and serum potassium concentrations after starting and during titration ▪ Use caution in patients who are at risk for excessive hypotension or have a serum creatinine level >3 mg/dL, serum potassium >5.0 mEq/L, or bilateral renal artery stenosis ▪ Should not be used in patients with a history of angioedema ▪ ACE inhibitor-induced angioedema is more likely to occur in Black patients ▪ Cough and angioedema can usually be relieved by replacing the ACE inhibitor with an ARB ▪ Fosinopril and perindopril are not FDA-approved for treatment of heart failure
Enalapril – generic ***Vasotec* (Bausch Health)**	2.5, 5, 10, 20 mg tabs	2.5 mg bid **Renal impairment:** CrCl ≤30 mL/min: 2.5 mg/day	10 mg bid	28.10 1144.20	
Fosinopril – generic	10, 20, 40 mg scored tabs	5-10 mg once/day **Renal impairment:** Moderate to severe: 5 mg/day	40 mg once/day	8.10	
Lisinopril – generic ***Prinivil* (Merck)** ***Zestril* (Almatica)**	2.5, 5, 10, 20, 40 mg tabs 5, 10, 20 mg tabs 2.5, 5, 10, 20, 30, 40 mg tabs	2.5-5 mg once/day **Renal impairment:** CrCl ≤30 mL/min: 2.5 mg/day	40 mg once/day	3.70 95.40 398.70	
Perindopril – generic	2, 4, 8 mg tabs	2 mg once/day **Renal impairment:** CrCl <30 mL/min: not recommended	16 mg once/day	40.50	
Quinapril – generic ***Accupril* (Pfizer)**	5, 10, 20, 40 mg tabs	5 mg bid **Renal impairment:** CrCl >30 mL/min: 5 mg/day; CrCl 10-30 mL/min: 2.5 mg/day	20 mg bid	17.50 292.00	
Ramipril – generic ***Altace* (Pfizer)**	1.25, 2.5, 5, 10 mg caps	1.25- 2.5 mg once/day **Renal impairment:** CrCl <40 mL/min: 25% of normal dose	10 mg once/day	39.90 220.80	
Trandolapril – generic	1, 2, 4 mg tabs	1 mg once/day **Renal impairment:** CrCl <30 mL/min: 0.5 mg/day	4 mg once/day	14.20	

ADVERSE EFFECTS

- Cough, angioedema, hypotension, renal impairment, and hyperkalemia can occur

DRUG INTERACTIONS

- Should not be used with an ARB or ARNI
- Use with potassium-sparing diuretics, renin inhibitors, trimethoprim/sulfamethoxazole, or other drugs that increase serum potassium concentrations increases the risk of hyperkalemia
- NSAIDs may decrease the effectiveness of ACE inhibitors and increase the risk of renal impairment
- ACE inhibitors can increase lithium serum concentrations; frequent monitoring is recommended
- Concurrent use of a thiopurine and an ACE inhibitor can cause leukopenia and anemia
- Captopril is a substrate of CYP2D6; use with a CYP2D6 inhibitor may increase its serum concentrations[7]
- Quinapril contains magnesium, which can decrease absorption of oral tetracyclines[8]

PREGNANCY and LACTATION

- Contraindicated for use during pregnancy because of an increased risk of fetal renal failure and death
- Low levels of some ACE inhibitors, including captopril, enalapril, perindopril, and quinapril, have been found in human breast milk, but no adverse effects are expected in breastfed infants

ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

- An ARNI is now preferred over an ACE inhibitor or ARB for patients with NYHA class II-IV heart failure. The benefits are most evident in those with HFrEF. In patients who are unable to tolerate an ARNI or cannot access an ARNI due to cost, an ACE inhibitor or ARB should be used instead.
- All patients with ACC/AHA Stage C (structural heart disease with prior or current heart failure symptoms) HFrEF should take, unless contraindicated, an ARNI (preferred), ACE inhibitor, or ARB, an evidence-based beta blocker, a MRA, and a SGLT2 inhibitor, and if volume overloaded, a diuretic.[1-3]

ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

DRUG	SOME ORAL FORMULATIONS	USUAL INITIAL ADULT DOSAGE	USUAL MAXIMUM ADULT DOSAGE	COST[4]	ADMINISTRATION/COMMENTS
Candesartan – generic ***Atacand*** **(AstraZeneca)**	4, 8, 16, 32 mg tabs	4-8 mg once/day	32 mg once/day	$75.30 298.00	▪ Long-term therapy reduces hospitalizations for heart failure and mortality in patients with HFrEF ▪ Can be used in patients who cannot tolerate an ACE inhibitor because of cough or angioedema or in patients who were already taking an ARB prior to the diagnosis of heart failure ▪ Should be started at low doses and titrated up to the highest tolerated dose, which is generally achieved by doubling the dose until the usual maximum daily dose is reached ▪ Monitor blood pressure, renal function, and serum potassium concentrations after starting and during titration ▪ Candesartan and valsartan are the only ARBs that are FDA-approved for treatment of heart failure; losartan has also been widely used
Losartan – generic ***Cozaar*** **(Merck)**	25, 50, 100 mg tabs	25-50 mg once/day **Hepatic impairment:** Mild to moderate: 25 mg/day Severe: not studied	150 mg once/day	14.00 333.90	
Valsartan – generic ***Diovan*** **(Novartis)**	40, 80, 160, 320 mg scored tabs[6]	20-40 mg bid	160 mg bid	40.50 506.80	

ADVERSE EFFECTS

- Hypotension, renal impairment, and hyperkalemia can occur
- Typically do not cause cough
- Probably do not cause angioedema

DRUG INTERACTIONS

- Should not be used with an ACE inhibitor or ARNI
- Use with potassium-sparing diuretics, renin inhibitors, trimethoprim/sulfamethoxazole, or other drugs that increase serum potassium concentrations increases the risk of hyperkalemia
- NSAIDs may decrease the effectiveness of ARBs and increase the risk of renal impairment
- ARBs can increase lithium serum concentrations; frequent monitoring is recommended
- Losartan is a substrate of CYP3A4 and CYP2C9; use with inducers of these isozymes could decrease its efficacy and use with inhibitors could increase its serum concentrations and toxicity[7]
- Valsartan is a substrate of OATP1B1; use with drugs that inhibit OATP1B1, such as atorvastatin, could increase valsartan serum concentrations[6]

PREGNANCY and LACTATION

- Contraindicated for use during pregnancy because of an increased risk of fetal renal failure and death
- No data on presence in breast milk

BETA-ADRENERGIC BLOCKERS

▶ All patients with ACC/AHA Stage C (structural heart disease with prior or current heart failure symptoms) HFrEF should take, unless contraindicated, an ARNI (preferred), ACE inhibitor, or ARB, an evidence-based beta blocker, a MRA, and a SGLT2 inhibitor, and if volume overloaded, a diuretic.[1-3]

BETA-ADRENERGIC BLOCKERS

DRUG	SOME ORAL FORMULATIONS	USUAL INITIAL ADULT DOSAGE	USUAL MAXIMUM ADULT DOSAGE	COST[4]	ADMINISTRATION/COMMENTS
Bisoprolol – generic	5, 10 mg tabs	1.25 mg once/day	10 mg once/day	$24.20	▪ Long-term therapy improves symptoms and clinical outcomes in patients with HFrEF ▪ Carvedilol, metoprolol succinate, and bisoprolol have been shown to reduce the rates of hospitalization for heart failure and death in patients with HFrEF ▪ Should be started at low doses and increased gradually, usually at 2-week intervals, to the highest tolerated dose ▪ Transient worsening of symptoms can occur following initiation of therapy, and full clinical benefits may not occur for 3-6 months or longer ▪ Monitor heart rate, blood pressure, and for signs of congestion after initiation and during titration ▪ Bisoprolol is not FDA-approved for treatment of heart failure
Carvedilol – generic	3.125, 6.25, 12.5, 25 mg tabs	3.125 mg bid	25 mg bid (>85 kg: 50 mg bid)	6.00 296.50	
***Coreg* (GSK)**					
extended-release – generic	10, 20, 40, 80 mg ER caps	10 mg once/day	80 mg once/day	213.70 275.30	
Coreg CR					
Metoprolol succinate – generic	25, 50, 100, 200 mg ER scored tabs[6]	12.5-25 mg once/day	200 mg once/day	22.50 94.20	
***Toprol-XL* (Aralez)**					

ADVERSE EFFECTS

- Fatigue, hypotension, bradycardia, asymptomatic fluid retention, and worsening heart failure may occur during the first few weeks of treatment; increasing the dose of concurrent diuretic may be helpful
- Carvedilol, which has vasodilatory activity, may cause more hypotension than metoprolol and bisoprolol
- Should be used cautiously, if at all, in patients with significant asthma or severe bradycardia; the risk of bronchospasm may be lower with metoprolol and bisoprolol because of their beta-1 selectivity

DRUG INTERACTIONS

- Carvedilol and metoprolol are substrates of CYP2D6; concurrent use of a CYP2D6 inhibitor may increase their serum concentrations and toxicity[7]
- Carvedilol is an inhibitor of the drug transporter P-gp and can increase concentrations of P-gp substrates, such as digoxin[7]
- Bisoprolol is a substrate of CYP3A4; use with CYP3A4 inducers may decrease its efficacy[7]

PREGNANCY and LACTATION

- Have been associated with fetal growth restriction, but beta-1-selective drugs (e.g., metoprolol, bisoprolol) are less likely to cause this effect
- Use during the first trimester has not been associated with an overall increase in congenital malformations, but in some studies, use in early pregnancy has been associated with increased rates of cleft lip/palate and cardiovascular and neural tube defects[9]
- Metoprolol is preferred in breastfeeding women; beta blockers with low protein binding (e.g., bisoprolol) are more likely to be excreted into breast milk and should be avoided

MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRAs)

▶ All patients with ACC/AHA Stage C (structural heart disease with prior or current heart failure symptoms) HFrEF should take, unless contraindicated, an ARNI (preferred), ACE inhibitor, or ARB, an evidence-based beta blocker, a MRA, and a SGLT2 inhibitor, and if volume overloaded, a diuretic.[1-3]

MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRAs)

DRUG	SOME ORAL FORMULATIONS	USUAL INITIAL ADULT DOSAGE	USUAL MAXIMUM ADULT DOSAGE	COST[4]	ADMINISTRATION/COMMENTS
Eplerenone – generic ***Inspra* (Pfizer)**	25, 50 mg tabs	Serum potassium ≤5 mEq/L and eGFR ≥50 mL/min/1.73 m^2: 25 mg once/day; eGFR 30-49 mL/min/1.73 m^2: 25 mg every other day; eGFR ≤30 mL/min/1.73 m^2: not recommended	Serum potassium ≤5 mEq/L and eGFR ≥50 mL/min/1.73 m^2: 50 mg once/day; eGFR 30-49 mL/min/1.73 m^2: 25 mg once/day; eGFR ≤30 mL/min/1.73 m^2: not recommended **Dosage adjustments based on serum potassium:** Serum potassium ≥6.0 mEq/L: withhold dose and restart at 25 mg every other day when levels fall to <5.5 mEq/L; 5.5-5.9 mEq/L: withhold dose if taking 25 mg every other day, reduce dose from 25 mg once daily to 25 mg every other day or from 50 to 25 mg once daily; 5.0-5.4 mEq/L: no adjustment <5.0 mEq/L: increase dose from 25 mg every other day to 25 mg once daily or from 25 to 50 mg once daily	$66.90 376.40	▪ Recommended for patients with NYHA class II-IV heart failure who have a LVEF ≤35%, a serum potassium level <5.0 mEq/L, and either an eGFR <30 mL/min/1.73 m^2 or a serum creatinine ≤2.5 mg/dL in men or ≤2.0 mg/dL in women ▪ When added to standard therapy in patients with HFrEF, have been shown to reduce the risk of hospitalization for heart failure and death ▪ Consider increasing dose at least every 2 weeks until maximum tolerated or target dose is achieved ▪ Eplerenone is similar in efficacy to spironolactone, but it costs more ▪ Monitor potassium and serum creatinine concentrations 2-3 days after starting, then again after 7 days, then monthly for 3 months, and then every 3 months thereafter during treatment
Spironolactone – generic ***Aldactone* (Pfizer)**	25, 50, 100 mg scored tabs	Serum potassium ≤5 mEq/L and eGFR ≥50 mL/min/1.73 m^2: 25 mg once/day; eGFR 30-49 mL/min/1.73 m^2: 25 mg every other day; eGFR ≤30 mL/min/1.73 m^2: not recommended **Dosage adjustments based on serum potassium:** Serum potassium is ≥5.5 mEq/L, withhold dose until levels are <5.0 mEq/L and consider restarting at a reduced dose	Serum potassium ≤5 mEq/L and eGFR ≥50 mL/min/1.73 m^2: 50 mg once/day; eGFR ≤30 mL/min/1.73 m^2: not recommended	12.90 134.50	

ADVERSE EFFECTS

- Hyperkalemia occurs frequently; the risk is higher in patients also taking an ARNI, ACE inhibitor, or ARB and in those with renal impairment
- Spironolactone has anti-androgenic activity and can cause erectile dysfunction and painful gynecomastia in men, menstrual irregularities in women, and hair loss in both men and women; the incidence of those effects is lower with eplerenone

DRUG INTERACTIONS

- Use with potassium-sparing diuretics, renin inhibitors, trimethoprim/sulfamethoxazole, or other drugs that increase serum potassium concentrations increases the risk of hyperkalemia
- Eplerenone is a substrate of CYP3A4. Use with CYP3A4 inducers could decrease its serum concentrations and efficacy and use with CYP3A4 inhibitors could increase its toxicity; concurrent use with strong CYP3A4 inhibitors is contraindicated[7]

PREGNANCY and LACTATION

- Teratogenic; should not be used during pregnancy
- Not recommended in breastfeeding women

SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS

▶ All patients with ACC/AHA Stage C (structural heart disease with prior or current heart failure symptoms) HFrEF should take, unless contraindicated, an ARNI (preferred), ACE inhibitor, or ARB, an evidence-based beta blocker, a MRA, and a SGLT2 inhibitor, and if volume overloaded, a diuretic.[1-3]

SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS

DRUG	SOME ORAL FORMULATIONS	USUAL INITIAL ADULT DOSAGE	USUAL MAXIMUM ADULT DOSAGE	COST[4]	ADMINISTRATION/COMMENTS
Dapagliflozin – *Farxiga* (AstraZeneca)[10]	5, 10 mg tabs	10 mg once/day **Renal impairment:** Initiation for glycemic control in patients with an eGFR <45 mL/min/1.73 m^2 is not recommended, but patients with chronic heart failure with an eGFR ≥30 mL/min/1.73 m^2 can take dapagliflozin to reduce the risk of cardiovascular death and hospitalization for heart failure[11]	10 mg once/day	$532.80	▪ Recommended for patients with NYHA class II-IV HFrEF and adequate renal function (≥30 mL/min/1.73 m^2 for dapagliflozin and eGFR ≥20 mL/min/1.73 m^2 for empagliflozin) ▪ Initially FDA-approved to improve glycemic control in patients with type 2 diabetes; all currently available SGLT2 inhibitors have been shown to reduce the risk of hospitalization by ~30% in such patients. ▪ In patients with HFrEF, with or without type 2 diabetes, dapagliflozin and empagliflozin have reduced a composite risk of hospitalization for heart failure or cardiovascular death ▪ Dapagliflozin and empagliflozin are the only SGLT2 inhibitors FDA-approved for use in heart failure ▪ Renal function should be assessed before starting treatment ▪ Should be taken in the morning to avoid nocturia ▪ Can be taken with or without food ▪ Correct volume depletion before starting ▪ Consider temporarily stopping in cases of reduced oral intake (such as acute illness or fasting) or fluid loss (such as gastrointestinal illness or excessive heat exposure)
Empagliflozin – *Jardiance* (Boehringer Ingleheim/Lilly)[12]	10, 25 mg tabs	10 mg once/day **Renal impairment:** Should not be used for glycemic control in patients with an eGFR ≤45 mL/min/1.73 m^2; but 10-mg once-daily doses in patients with an eGFR ≥20 mL/min/1.73 m^2 have had renal and cardiac benefits[13]	10 mg once/day	548.50	

ADVERSE EFFECTS

▪ Urinary tract infections and genital mycotic infections are the most common adverse effects
▪ Fournier's gangrene can occur

DRUG INTERACTIONS

▪ Hypoglycemia has occurred when used in combination with insulin and sulfonylureas

PREGNANCY and LACTATION

▪ Not recommended during the second and third trimesters of pregnancy based on adverse renal effects in animals
▪ Not recommended in breastfeeding women

DRUGS FOR TREATMENT OF HFrEF (continued)

LOOP DIURETICS

▶ All patients with ACC/AHA Stage C (structural heart disease with prior or current heart failure symptoms) HFrEF should take, unless contraindicated, an ARNI (preferred), ACE inhibitor or ARB, an evidence-based beta blocker, a MRA, and a SGLT2 inhibitor, and if volume overloaded, a diuretic.[1-3]

LOOP DIURETICS

DRUG	SOME ORAL FORMULATIONS	USUAL INITIAL ADULT DOSAGE	USUAL MAXIMUM ADULT DOSAGE	COST[4]	ADMINISTRATION/COMMENTS
Bumetanide – generic	0.5, 1, 2 mg tabs	0.5-1 mg once/day or bid	10 mg once/day or in divided doses	$162.40	▪ Most patients with heart failure have fluid retention; in such patients, diuretics relieve symptoms, but their effect on survival is unclear ▪ Provide symptomatic relief of pulmonary and peripheral edema more rapidly than other drugs used for treatment of heart failure ▪ Loop diuretics are more effective than thiazide diuretics in patients with heart failure ▪ Bumetanide and torsemide have longer half-lives and are better absorbed than furosemide, but there is no clinical evidence that either is more effective ▪ Should be started at a low dose, which can be titrated upward until urine output increases and weight decreases ▪ Higher starting doses can be used in patients with renal impairment or prior refractoriness to loop diuretics ▪ IV administration, concurrent use of 2 diuretics (a loop and a thiazide-like diuretic) or addition of a MRA can sometimes overcome diuretic resistance ▪ Monitor blood pressure, renal function, and electrolytes after starting and during titration
Furosemide – generic ***Lasix* (Validus)**	20, 40, 80 mg tabs	20-40 mg once/day or bid	600 mg once/day or in divided doses	27.20 493.70	
Torsemide – generic	5, 10, 20, 100 mg tabs	10-20 mg once/day	200 mg once/day or in divided doses	49.40	

ADVERSE EFFECTS

- The most common adverse effect is hypokalemia
- Can also cause worsening of renal function

DRUG INTERACTIONS

- NSAIDs can decrease the effectiveness of diuretics
- Concurrent use of lithium and a diuretic could increase lithium serum concentrations; frequent monitoring is recommended
- Torsemide is a substrate of CYP2C9; use with inducers of CYP2C9 could decrease its efficacy and use with CYP2C9 inhibitors could increase serum concentrations and toxicity[7]

PREGNANCY and LACTATION

- Should be initiated with caution during pregnancy because these drugs cause volume depletion during their first weeks of use and may reduce uteroplacental perfusion; women already taking a diuretic who become pregnant can generally continue taking it
- Decrease in fluid volume may impact lactation; diuretics have been used to intentionally suppress lactation
- No data on presence of loop diuretics in breast milk
- Thiazide diuretics are present in breast milk in low concentrations; no adverse effects are expected in breastfed infants

DRUGS FOR TREATMENT OF HFrEF (continued)

VASODILATORS

- Black patients with HFrEF, especially those with persistent NYHA class III-IV symptoms despite use of target or maximally tolerated doses of an ARNI, ACE inhibitor, or ARB, a beta blocker, and an MRA, can benefit from addition of isosorbide dinitrate and hydralazine.[1-3]

VASODILATORS

DRUG	SOME ORAL FORMULATIONS	USUAL INITIAL ADULT DOSAGE	USUAL MAXIMUM ADULT DOSAGE	COST[4]	ADMINISTRATION/COMMENTS
Isosorbide dinitrate/ hydralazine – *BiDil* (Arbor)	20/37.5 mg tabs	20/37.5 mg tid	40/75 mg tid	$610.10	▪ When added to standard heart failure therapy, the combination has been shown to reduce the rate of first hospitalization for heart failure and improve survival ▪ Benefit in non-Black patients is less well established, but use of the combination can be considered in those who cannot tolerate an ARNI, ACE inhibitor, or ARB ▪ Should be started at a low dose, which can be titrated upward every 2-4 weeks ▪ Monitor for hypotension after starting and during titration
Isosorbide dinitrate – Generic	5, 10, 20, 30, 40 mg tabs	20-30 mg tid	40 mg tid	141.20	
Hydralazine – generic	10, 25, 50, 100 mg tabs	20-50 mg tid	100 mg tid	23.80	

ADVERSE EFFECTS

- Hypotension, headache, and dizziness can occur
- Hydralazine alone can cause tachycardia, peripheral neuritis, and a lupus-like syndrome

DRUG INTERACTIONS

- Concurrent use of phosphodiesterase 5 (PDE5) inhibitors such as sildenafil is not recommended because of the risk of additive hypotensive effects[8]

PREGNANCY and LACTATION

- No data are available on its safety for use during pregnancy
- No data on presence in breast milk

I_f CHANNEL BLOCKER

▶ In patients with NYHA class II-III heart failure and a LVEF ≤35% who are in sinus rhythm with a resting heart rate ≥70 bpm despite use of target or maximally tolerated doses of a beta blocker, addition of the I_f channel inhibitor ivabradine should be considered.[1-3]

I_f CHANNEL BLOCKER

DRUG	SOME ORAL FORMULATIONS	USUAL INITIAL ADULT DOSAGE	USUAL MAXIMUM ADULT DOSAGE	COST[4]	ADMINISTRATION/COMMENTS
Ivabradine – *Corlanor* (Amgen)	5 mg scored tabs, 7.5 mg tabs	5 mg bid 2.5 mg bid is recommended for patients with underlying conduction defects or in those at higher risk of hemodynamic compromise **Hepatic impairment:** Severe (Child-Pugh C): contraindicated	7.5 mg bid (titrate to heart rate 50-60 bpm)	$491.50	▪ Slows heart rate in patients in sinus rhythm by inhibiting the cardiac pacemaker I_f current ▪ Has no effect on contractility ▪ In patients with symptomatic heart failure, a LVEF ≤35% and a resting heart rate ≥70 bpm despite use of target or maximally-tolerated beta blocker therapy, addition of ivabradine significantly reduced the rates of hospitalization for worsening heart failure and death due to heart failure, but not cardiovascular death, compared to placebo. The patients in the trial were not receiving maximally tolerated beta blocker therapy.[14] ▪ Taken with food ▪ The dose should be adjusted every 2 weeks, targeted to a heart rate of 50-60 bpm

ADVERSE EFFECTS

- Symptomatic bradycardia, hypertension, atrial fibrillation, and visual effects (transient increases in brightness due to inhibition of electric currents in the retina) have been reported
- Should not be used in patients with atrial fibrillation

DRUG INTERACTIONS

- Ivabradine is a substrate of CYP3A4; use with strong CYP3A4 inhibitors is contraindicated and use with 3A4 inducers or moderate 3A4 inhibitors should be avoided[7]

PREGNANCY and LACTATION

- Fetal toxicity and cardiac teratogenic effects have occurred in animal studies; women of childbearing age should use effective contraception while taking ivabradine
- Pregnant women taking ivabradine should be monitored for bradycardia, destabilization of heart failure, and preterm birth (in the third trimester)
- Breastfeeding should be avoided

SOLUBLE GUANYLATE CYCLASE (sGC) STIMULATOR

▶ In patients with symptomatic heart failure and a LVEF <45% who were recently hospitalized or required treatment with an IV diuretic, addition of the soluble guanylate cyclase (sGC) stimulator vericiguat modestly reduced the composite risk of first hospitalization for heart failure or cardiovascular death, but not the risk of cardiovascular death alone.[15]

SOLUBLE GUANYLATE CYCLASE (sGC) STIMULATOR

DRUG	SOME ORAL FORMULATIONS	USUAL INITIAL ADULT DOSAGE	USUAL MAXIMUM ADULT DOSAGE	COST[4]	ADMINISTRATION/COMMENTS
Vericiguat – *Verquvo* (Merck)	2.5, 5, 10 mg tabs	2.5 mg once/day	10 mg once/day	$582.90	▪ FDA-approved to reduce the risk of hospitalization for heart failure and cardiovascular death following a worsening heart failure event (hospitalization for heart failure or treatment with IV diuretics) in patients with symptomatic heart failure and a LVEF <45%. ▪ Binds to and stimulates sGC independently of and combined with endogenous nitric oxide to increase production of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation and vasodilation. ▪ In one clinical trial (VICTORIA), addition of vericiguat to standard therapy that generally did not include an ARNI or SGLT2 inhibitor modestly reduced the risk of a composite of cardiovascular death or first hospitalization for heart failure. The effect was primarily on hospitalization; cardiovascular death as a lone endpoint was not reduced. ▪ Taken with food ▪ The daily dose should be doubled every 2 weeks as tolerated up to a target of 10 mg

ADVERSE EFFECTS

▪ In the clinical trial, anemia occurred in 10% of patients who received vericiguat compared to 7% who received placebo

DRUG INTERACTIONS

▪ Concurrent use of phosphodiesterase-5 (PDE5) inhibitors such as sildenafil is not recommended because of the risk of additive hypotensive effects[8]

PREGNANCY and LACTATION

▪ Administration of vericiguat to pregnant animals resulted in cardiac malformations, increased abortions and resorptions, decreased pup weight, and increased mortality; contraindicated for use during pregnancy
▪ An effective form of contraception is recommended during treatment and for one month after stopping vericiguat
▪ Breastfeeding should be avoided

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