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Drug Class Literature Scan: Newer Drugs for Heart Failure

Date of Review: August 2026

Date of Last Review: June 2022 (Diuretics, Oral)
Feb 2022 (Inhibitors of the Renin-Angiotensin-Aldosterone System)
Literature Search: 01/01/22 – 03/31/2026

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This literature scan looks at recently published evidence for medicines used to treat heart failure. When the heart muscle cannot pump as well as it should to meet the body's needs for nutrients and oxygen from the blood, it is called heart failure. Heart failure may be caused by many different things. Examples are increased blood pressure (hypertension), damaged heart valves, coronary artery disease, irregular heartbeat, a heart attack, and inflammation of the heart muscle.
- Symptoms of heart failure include feeling tired, shortness of breath, coughing, swelling in the legs, ankles, or feet, and rapid weight gain because not enough fluid is removed from the body. Everyday activities such as walking or climbing stairs can become very difficult.
- There are many medicines used to treat the symptoms of heart failure, and they work in different ways to improve the heart's ability to pump blood to the rest of the body. People with heart failure often need more than one medicine to treat their symptoms.
- Diuretics are medicines that decrease the amount of the blood the heart must pump by removing extra sodium and fluid from the body. Diuretics used to treat heart failure include furosemide, torsemide, and bumetanide.
- Spironolactone and finerenone block the effects of aldosterone, a hormone that controls the body's release of sodium and water. These medicines help decrease blood pressure and decrease fluid buildup (edema).
- Other medicines used to treat heart failure relax the blood vessels to make it easier for the heart to pump blood. These medicines are called angiotensin converting enzyme (ACE) inhibitors (e.g., lisinopril, enalapril) and angiotensin II receptor blockers (ARBs) (e.g., losartan, valsartan). Sacubitril/valsartan can replace an ACE inhibitor or ARB in the treatment of heart failure. It is a combination medicine called an angiotensin-receptor neprilysin inhibitor (ARNi). This medicine can improve blood flow, reduce extra fluids in the body, and decrease the strain on the heart.
- Vericiguat is a newer medicine approved for adults after being discharged from the hospital for treatment of heart failure symptoms. When taken with other heart failure medicines, vericiguat can decrease the risk of future hospital admissions and dying from heart failure complications.
- Sodium-glucose costransporter-2 (SGLT-2) inhibitors (i.e., empagliflozin, dapagliflozin), are approved to lower blood sugar in people with diabetes. These medicines have also been shown to reduce hospitalizations due to heart failure symptoms.
- The use of finerenone, vericiguat, and SGLT-2 inhibitors have been added as recommendations to the latest heart failure treatment guidelines.
- Oregon Health Plan provides coverage for several diuretics, ACE inhibitors, and ARBs including furosemide, spironolactone, bumetanide, chlorthalidone, torsemide, ramipril, quinapril, candesartan, irbesartan, benazepril, olmesartan, losartan, valsartan, enalapril, and lisinopril. For all other heart failure

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medicines, including sacubitril/valsartan, finerenone, vericiguat, and SGLT2 inhibitors, the provider must submit documentation why the patient needs the medicine. This process is called prior authorization.

Conclusions:

- Three high-quality systematic reviews[1-3] and 5 high-quality clinical guidelines[4-8] have been published since the last Pharmacy and Therapeutics (P and T) review of guideline-directed medical therapy (GDMT) for heart failure.
- A 2025 systematic review and meta-analysis of comparative randomized controlled trials (RCTs) of furosemide and torsemide assessed differences in clinical outcomes in patients treated with these diuretics for management of heart failure.[1] Moderate-quality evidence from pooled RCTs, showed that torsemide compared with furosemide did not result in a statistically significant difference in all-cause mortality or all cause rehospitalization rates in patients with heart failure.[1]
- A 2023 systematic review and meta-analysis evaluated the association of ARNis with atherosclerotic cardiovascular disease (ASCVD) events in patients with heart failure.[2] The major findings from moderate-quality evidence were as follows: (1) the incidence of ASCVD events was not significantly different between patients with heart failure receiving ARNi therapy versus those receiving ACE inhibitor/ARB therapy; (2) patients with heart failure receiving ARNi therapy had a higher incidence of peripheral artery disease compared to patients treated with ACE inhibitor/ARB therapy (risk ratio [RR] 1.63, 95% confidence interval [CI] 1.05 to 2.52, p = 0.03); and (3) findings were generally consistent when stratified by ACE inhibitor/ARB type, length of follow-up, and type of heart failure based on ejection fraction.[2]
- A 2021 Cochrane review assessed the effects of beta-blockers, ACE inhibitors, ARBs, ARNis, and mineralocorticoid receptor antagonists (MRAs) in people with heart failure and preserved ejection fraction (HFpEF).[3] There is moderate certainty evidence that MRA and ARNi treatment in HFpEF probably reduces heart failure hospitalization compared to placebo/usual care but probably has little or no effect on cardiovascular (CV) mortality (moderate certainty evidence) and quality of life (high certainty evidence).[3] Low certainty evidence shows beta-blocker treatment may reduce the risk of CV mortality compared to placebo/usual care.[3] Although MRAs and ARNis are probably effective at reducing the risk of heart failure hospitalization (moderate certainty evidence), the treatment effect sizes are modest.[3]
- In recently published guidance (2026), Canada's Drug Agency (CDA) recommends that finerenone be reimbursed by public drug plans as an add-on to standard of care in adults with heart failure with left ventricular ejection fraction (LVEF) ≥ 40% to reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visits.[4]
- Guidance from CDA (2023) recommends that vericiguat be reimbursed for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent heart failure decompensation event requiring hospitalization and/or intravenous (IV) diuretic therapy.[5]
- Recommendations for treating heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and HFpEF were revised in the updated National Institute for Health and Care Excellence (NICE) guidance for management of adults with chronic heart failure in 2025.[6] Recommendations include:
    - Offer an ACE inhibitor, beta-blocker, MRA, and SGLT2 inhibitor to people with HFrEF.[6]
    - Consider an ACE inhibitor, beta-blocker, MRA, and SGLT2 inhibitor to people with HFmrEF.[6]
    - For people who have an intolerance to an ACE inhibitor, or if the ACE inhibitor is ineffective at maximally tolerated doses, consider switching to an ARB or ARNi.[6]
- Focused guidance was developed by the European Society of Cardiology (ESC) in 2023.[7] Recommendations for the use of SGLT2 inhibitors and finerenone in heart failure management were added to the treatment recommendations.[7]

- The 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guideline consolidated 2013 and 2017 recommendations into a new document along with recently published evidence for updated heart failure treatment strategies.[8] Pharmacologic recommendations for management of HFrEF, HFmrEF, and HFpEF are presented in **Tables 1, 2, and 3,** respectively. Recent changes include:
- Guideline-directed medical therapy (GDMT) for HFrEF includes the following 4 medication classes: renin-angiotensin-aldosterone system (RAAS) inhibitors/ARNis, beta blockers, MRAs, and SGLT2 inhibitors.[8]
- SGLT2 inhibitors are strongly recommended in HFmrEF. Weaker recommendations are made for ARNi, ACE inhibitor, ARB, MRA, and beta blocker therapy for patients with HFmrEF.[8]
- New recommendations for treatment of HFpEF are made for SGLT2 inhibitors, MRAs, and ARNis.[8]
- Heart failure with improved LVEF (HFimpEF) refers to patients with previous HFrEF who now have an LVEF > 40%. These patients should continue their HFrEF treatment.[8]
- New formulations approved by the Food and Drug Administration (FDA) include:
    - 10/2025: LASIX ONYU is a single-use, subcutaneous injection form of furosemide designed to administer 80 mg over 5 hours via an infusion device.[9] LASIX ONYU is indicated for the treatment of edema in adult patients with heart failure.[9]
    - 9/2025: ENBUMYST is a new dosage form of bumetanide nasal spray which contains 0.5 mg/0.1 mL per each unit of use device.[10] ENBUMYST is indicated for the treatment of edema associated with congestive heart failure, hepatic cirrhosis, and renal disease, including nephrotic syndrome in adults.[10]
    - 7/2025: VOSTALLY is a new dosage form of ramipril oral suspension 1 mg/mL, indicated for the treatment of hypertension in adults; to reduce the risk of myocardial infarction (MI), stroke or death from CV causes in patients 55 years or older at high risk of developing major CV events; and to reduce the risk of CV death and hospitalization for heart failure in adults with post-MI heart failure.[11]
    - 3/2025: ARBLI, a new dosage form of losartan oral suspension 10 mg/mL, is indicated for the treatment of hypertension in adults and children greater than 6 years old; reduction of stroke in patients with hypertension and left ventricular hypertrophy (there is evidence that this benefit does not apply to Black patients); and treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes mellitus (T2DM) and a history of hypertension.[12]
    - 3/2025: HEMICLOR, a new oral dosage form of chlorthalidone 12.5 mg tablets, is indicated for the treatment of hypertension in adults.[13] The manufacturer did not conduct any clinical studies for this dosage form, instead a literature-based review was submitted to the FDA to support the efficacy of 12.5 mg dosing of chlorthalidone to control hypertension alone or in combination with other antihypertensive medications.[13]
    - 1/2025: INZIRQO, a new dosage form of hydrochlorothiazide oral suspension 10 mg/mL, is indicated for the treatment of hypertension in adults and pediatric patients and for the treatment of edema associated with congestive heart failure, hepatic cirrhosis, and renal disease in adults and pediatrics.[14]
    - 10/2022: FUROSCIX, a single-use, subcutaneous injection form of furosemide is designed to administer 80 mg over 5 hours.[15] FUROSCIX is indicated for the treatment of congestion due to fluid overload in adults with New York Heart Association (NYHA) Class II/III chronic heart failure.[15]
- New FDA-approved indications include:
    - 12/2025: The expanded use of FUROSCIX for the treatment of edema in pediatric patients weighing 43 kg and above with chronic heart failure.[15] Previously, FUROSCIX was FDA-approved for treatment of edema in adults with chronic heart failure or chronic kidney disease (CKD), including nephrotic syndrome.[7] (The CKD indication was added in March 2025.[7]) FUROSCIX has not been studied in pediatric patients.[15] Use of FUROSCIX in pediatric patients is supported by efficacy, safety, and pharmacokinetic data of IV furosemide in adults.[15]

- 7/2025: An expanded indication of finerenone for reduction of risk of CV death, hospitalization for heart failure, and urgent heart failure visits in adults with heart failure and LVEF ≥ 40%.[16] Prior to this expanded indication, finerenone was approved to reduce the risk of sustained estimated glomerular filtration (eGFR) decline, end stage kidney disease, CV death, non-fatal MI and hospitalization for heart failure in adults with CKD associated with type 2 diabetes mellitus (T2DM).[16] The safety and efficacy of finerenone in patients with heart failure was evaluated in a double-blind, placebo-controlled, multicenter RCT.[16] The primary endpoint was the composite of CV death and total (first and recurrent) heart failure events comprised of hospitalization for heart failure and urgent heart failure visits.[16] Finerenone reduced the risk of the primary composite endpoint compared to placebo (RR 0.84; 95% CI 0.74 to 0.95; p = 0.007).[16] The overall safety profile of finerenone in this study was largely consistent with the adverse reactions reported in patients with CKD and T2DM.[16]
- 4/2021: Expanded approval of valsartan to include children aged 1 year and older for the treatment of hypertension.[17] Previously, the treatment was indicated for patients 6 years of age and older with hypertension.[17] The antihypertensive effects of valsartan were evaluated in 3 single-arm clinical studies in pediatric patients aged 1 to 5 years.[17] In all 3 RCTs, valsartan reduced systolic blood pressure.[17] The adverse event profile of valsartan in children was similar to adverse events reported in adult studies.[17]

Recommendations:

- Rename "Diuretics, Oral" to "Diuretics, Outpatient" to accommodate new subcutaneous and nasal formulations intended for outpatient use.
- Revise finerenone prior authorization (PA) criteria to include use in the expanded FDA-approved indication to reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visits in patients with LVEF ≥ 40%.
- Maintain the following new formulations of diuretics and RAAS inhibitors as nonpreferred on the preferred drug list (PDL): chlorthalidone 12.5 mg tablet (HEMICLOR); subcutaneous forms of furosemide (FUROSCIX, LASIX ONYU); oral suspensions and oral solutions of HCTZ, losartan, and ramipril (INZIRQO, ARBLI, VOSTALLY); and bumetanide nasal spray (ENBUMYST). Make a metolazone product preferred based upon AHA the recommendation that metolazone or chlorothiazide may be added to loop diuretics in patients with heart failure and refractory edema unresponsive to loop diuretics alone.[8]
- Based on guideline recommendations that support the use of ARNIs (sacubitril/valsartan) as part of GDMT in heart failure, retire PA criteria for sacubitril/valsartan.
- Evaluate medication costs in executive session.

Summary of Prior Reviews and Current Policy

- At the June 2022 meeting the Pharmacy and Therapeutics (P & T) Committee evaluated evidence for the safety and efficacy of diuretics for the prevention of mortality and CV disease in patients with hypertension, heart failure, and CKD. In addition, evidence for a new selective MRA, finerenone, was reviewed. No changes to the PDL were made based on the clinical evidence presented at the meeting. Finerenone was maintained as non-preferred on the PDL with prior authorization (PA) to limit use to patients with CKD and T2DM on background therapy with an ACE inhibitor or ARB (see **Appendix 6**).
- At the February 2022 P & T Committee meeting the committee reviewed evidence for RAAS inhibitors. After review of evidence and evaluation of costs in executive session, fosinopril, quinapril, and candesartan were made preferred on the PDL.
- At the June 2021 P & T Committee meeting evidence was presented for vericiguat, a soluble guanylate stimulator, indicated to reduce the risk of CV death and hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic heart failure and LVEF less than 45%. The committee accepted the recommendation to maintain vericiguat as non-preferred on the PDL and require PA to ensure appropriate use in patients on goal directed therapy with advanced symptomatic HFrEF (see **Appendix 6**).

- Preferred agents in the oral diuretic class include tablet and capsule formulations of hydrochlorothiazide (HCTZ), triamterene, triamterene/HCTZ, furosemide, spironolactone, amiloride, amiloride/HCTZ, bumetanide, chlorthalidone, indapamide, spironolactone/HCTCZ, and torsemide (see **Appendix 1**). All other diuretics and formulations are subject to nonpreferred PA criteria.
- Preferred agents in the RAAS inhibitor drug class include fosinopril, ramipril, quinapril, candesartan, irbesartan, benazepril, olmesartan, losartan, valsartan, enalapril, lisinopril, telmisartan (see **Appendix 1**). All other RAAS inhibitors are subject to nonpreferred PA criteria.
- Current PA criteria limit use of sacubitril/valsartan to patients with heart failure and LVEF less than 40%, on maximally tolerated ACE inhibitor or ARB and a recommended beta-blocker with evidence of efficacy and safety in patients with heart failure (see **Appendix 6**).

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Furosemide Versus Torsemide on Hospitalizations and Mortality in Patients With Heart Failure (2025)
A systematic review and meta-analysis of comparative RCTs of furosemide and torsemide assessed differences in clinical outcomes in patients treated with these diuretics for management of patients with any type of heart failure.[1] Literature was searched through August 5, 2023 and 188 studies were initially identified.[1] Only the RCTs comparing furosemide and torsemide in adult patients with heart failure that measured mortality and hospitalizations were included in the analysis.[1] Twelve RCTs met inclusion criteria with a total of 5,424 patients.[1] Ten of the 12 studies were open-label RCTs, which increased the risk of bias.[1] Otherwise, the risk of bias in other domains was low.[1]

There was no significant difference in all-cause mortality between furosemide and torsemide (RR 0.98; 95% CI 87 to 1.10; p = 0.73; 9 RCTs; moderate-quality evidence).[1] Pooled analysis of RCTs that assessed the risk for rehospitalization did not show any statistically significant difference between torsemide and furosemide groups (RR 0.95, 95% CI 0.88 to 1.02; p = 0.16; 7 RCTs; moderate-quality evidence).[1] In summary, considering the moderate-quality evidence from pooled RCTs, torsemide compared with furosemide did not result in a statistically significant difference in all-cause mortality or all cause rehospitalization rates in patients with heart failure.

Angiotensin Receptor-Neprilysin Inhibitor Effects on Atherosclerotic Cardiovascular Disease Events (2023)
This systematic review and meta-analysis evaluated the association of ARNis with ASCVD events in patients with heart failure.[2] Literature was searched through January 4, 2023 for studies comparing ARNis with ACE inhibitors or ARBs in terms of MI, stroke, angina pectoris, peripheral artery disease, and the composite end point of all 4 events in patients with HF.[2] A total of 8 RCTs met inclusion criteria, with 17,541 patients assigned to either the ARNi (n=8,764) or ACE

inhibitor/ARB (n=8,777) groups.[2] Five RCTs included patients with HFrEF and 3 studies included only patients with HFpEF.[2] The ACE inhibitors and ARBs used in the control group were enalapril in 5 studies, valsartan in 2 studies, and enalapril/valsartan in one trial.[2] The follow-up durations ranged from 8 weeks to 35 months.[2] Six RCTs were identified as having moderate risk of bias and 2 RCTs were identified as having a low risk of bias.[2] There was no study with a high risk of bias in any domain.[2]

The incidence of composite end point (RR 1.03, 95% CI 0.93 to 1.13, p = 0.63), MI (RR 1.02, 95% CI 0.81 to 1.30, p = 0.85), angina pectoris (RR 0.96, 95% CI 0.80 to 1.17, p = 0.70), and stroke (RR 0.99, 95% CI 0.85 to 1.16, p = 0.93) were not statistically different between the ARNi and ACE inhibitor/ARB groups.[2] However, ARNi therapy was associated with a higher incidence of peripheral artery disease (RR 1.63, 95% CI 1.05 to 2.52, p = 0.03).[2] In the subgroup analyses for the composite end point of MI, stroke, angina, or peripheral artery disease, there was no statistical difference between groups according to the type of ACE inhibitor/ARB used (enalapril [RR 0.99, 95% CI 0.85 to 1.16, p = 0.95, I^2 = 10%] or valsartan [RR 1.05, 95% CI 0.92 to 1.21, p = 0.47, I^2 = 0%] compared to ARNi therapy.[2] There was no statistical difference between groups for the length of follow-up (8 to 12 weeks [RR 0.73, 95% CI 0.19 to 2.74, p = 0.64, I^2 = 35%]; 24 to 36 weeks [RR 0.96, 95% CI 0.50 to 1.81, p = 0.89, I^2 = 0%]; and 108 to 140 weeks [RR 1.03, 95% CI 0.93 to 1.14, p = 0.57, I^2 = 0%;].[2] There was no statistical difference between ARNi vs ACE inhibitor/ARB for the classification of the heart failure based on ejection fraction (HFpEF [RR 0.99, 95% CI 0.86 to 1.16, p = 0.94, I^2 = 0%] and HFrEF [RR 1.05, 95% CI 0.92 to 1.20, p = 0.47, I^2 = 7%]).[2]

In summary, for this meta-analysis the major findings from moderate-quality evidence were as follows: (1) the incidence of ASCVD events was not significantly different between patients with heart failure receiving ARNi therapy versus those receiving ACE inhibitor/ARB therapy; (2) patients with heart failure receiving ARNi therapy had a higher incidence of peripheral artery disease compared to patients treated with ACE inhibitor/ARB therapy (RR 1.63, 95% CI 1.05 to 2.52, p = 0.03); and (3) findings were generally consistent when stratified by ACE inhibitor/ARB type, length of follow-up, and heart failure based on ejection fraction.[2]

Beta-Blockers and Inhibitors Of The Renin-Angiotensin Aldosterone System For Chronic Heart Failure With Preserved Ejection Fraction (2021)

A Cochrane review assessed the effects of beta-blockers, ACE inhibitors, ARBs, ARNis, and MRAs in people with HFpEF.[3] Literature was searched through May 2020 and 41 RCTs met inclusion criteria.[3] The risk of bias was frequently unclear and only 5 studies had a low risk of bias in all domains.[3]

<u>Beta-blockers</u>

Ten studies (n=3087) investigated beta-blockers. Five studies used a placebo comparator and in 5 studies the comparator was usual care.[3] The age of participants ranged from 30 years to 81 years.[3] A possible reduction in CV mortality was observed with beta-blockers compared to placebo/usual care (RR 0.78, 95% CI 0.62 to 0.99; number needed to treat for an additional benefit (NNTB) 25; n=1046; 3 studies), however, the certainty of evidence was low.[3] There may be little to no effect on all-cause mortality (RR 0.82, 95% CI 0.67 to 1.00; n=1105; 4 studies; low-certainty evidence).[3] The effects on heart failure hospitalization, hyperkalemia, and quality of life remain uncertain.[3]

<u>Mineralocorticoid Receptor Antagonists</u>

Thirteen studies (n = 4459) investigated MRAs in HFpEF.[3] Eight studies used a placebo comparator and in 5 studies the comparator was usual care.[3] The age of participants ranged from 54.5 to 80 years.[3] Pooled analysis indicated that MRA treatment probably reduces heart failure hospitalization compared to placebo/usual care (RR 0.82, 95% CI 0.69 to 0.98; NNTB = 41; n= 3714; 3 studies; moderate-certainty evidence).[3] However, MRA treatment probably has little or no effect on all-cause mortality compared to placebo/usual care (RR 0.91, 95% CI 0.78 to 1.06; n=4207; 5 studies; moderate-certainty evidence) and cardiovascular mortality (RR 0.90, 95% CI 0.74 to 1.11; n=4070; 3 studies; moderate-certainty evidence).[3] MRA treatment may have little or no effect on quality of life measures compared to placebo/usual care (mean difference [MD] 0.84, 95% CI -2.30 to 3.98; n=511; 3 studies; low-certainty evidence).[3] MRA treatment

was associated with a higher risk of hyperkalemia compared to placebo/usual care (RR 2.11, 95% CI 1.77 to 2.51; number needed to treat for an additional harmful outcome [NNTH] = 11; n=4291; 6 studies; high-certainty evidence).[3]

Angiotensin-Converting Enzyme Inhibitors

Eight studies (n = 2061) investigated ACE inhibitors.[3] Three studies used a placebo comparator and in 5 studies the comparator was usual care.[3] The mean age of participants ranged from 70 to 82 years.[3] Pooled analyses with moderate-certainty evidence suggest that ACE inhibitor treatment likely has little or no effect on cardiovascular mortality compared to placebo/usual care (RR 0.93, 95% CI 0.61 to 1.42; n=945; 2 studies), all-cause mortality (RR 1.04, 95% CI 0.75 to 1.45; n=1187; 5 studies) and heart failure hospitalization (RR 0.86, 95% CI 0.64 to 1.15; n=1019; 3 studies), and may result in little or no effect on the quality of life (MD -0.09, 95% CI -3.66 to 3.48; n=154; 2 studies; low-certainty evidence).[3] The effects of ACE inhibitors on hyperkalemia remain uncertain.[3]

Angiotensin Receptor Blockers

Eight studies (n = 8755) investigating ARBs were included.[3] Five studies used a placebo comparator and in 3 studies the comparator was usual care.[3] The mean age of participants ranged from 61 to 75 years.[3] Pooled analyses with high certainty of evidence suggest that ARB treatment has little or no effect on cardiovascular mortality compared to placebo/usual care (RR 1.02, 95% 0.90 to 1.14; n=7254; 3 studies), all-cause mortality (RR 1.01, 95% CI 0.92 to 1.11; n=7964; 4 studies), heart failure hospitalization (RR 0.92, 95% CI 0.83 to 1.02; n=7254; 3 studies), and quality of life (MD 0.41, 95% CI -0.86 to 1.67; n=3117; 3 studies).[3] ARBs were associated with a higher risk of hyperkalemia compared to placebo/usual care (RR 1.88, 95% CI 1.07 to 3.33; n=7148; 2 studies; high-certainty evidence).[3]

Angiotensin Receptor Neprilysin Inhibitors

Three studies (n = 7702) investigating ARNis were included.[3] Two studies used ARBs as the comparator and one used standardized medical therapy, based on participants' established treatments at enrollment.[3] The mean age of participants ranged from 71 to 73 years.[3] Results suggest that ARNis may have little or no effect on cardiovascular mortality compared to ARBs/standard medical therapy (RR 0.96, 95% CI 0.79 to 1.15; n=4796; one study; moderate-certainty evidence), all-cause mortality (RR 0.97, 95% CI 0.84 to 1.11; n=7663; 3 studies; high-certainty evidence), or quality of life (high-certainty evidence).[3] However, ARNi treatment may result in a slight reduction in heart failure hospitalization, compared to usual care (RR 0.89, 95% CI 0.80 to 1.00; n=7362; 2 studies; moderate-certainty evidence).[3] ARNi treatment was associated with a reduced risk of hyperkalemia compared with valsartan (RR 0.88, 95% CI 0.77 to 1.01; n=5054; 2 studies; moderate-certainty evidence).[3]

In summary, there is moderate certainty evidence that MRA and ARNi treatment in HFpEF probably reduces heart failure hospitalization but probably has little or no effect on cardiovascular mortality and quality of life (high-quality evidence) compared to placebo/usual care.[3] Low certainty evidence shows beta-blocker treatment may reduce the risk of cardiovascular mortality compared to placebo/usual care; however, further trials are needed.[3] The current evidence for beta-blockers, ACE inhibitors, and ARBs is limited and does not support their use in HFpEF in the absence of an alternative indication.[3] Although MRAs and ARNIs are probably effective at reducing the risk of heart failure hospitalization (moderate certainty evidence), the treatment effect sizes are modest.[3]

After review, 29 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), network meta-analysis, comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

Canada's Drug Agency: Finerenone Reimbursement Recommendation (2026)
Canada's Drug Agency (CDA) recommends that finerenone be reimbursed by public drug plans as an add-on to standard of care in adults with heart failure with LVEF ≥ 40% to reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visits.[4] Finerenone should only be covered when initiated as an add-on to standard of care therapy in adults with NYHA class II to IV with mildly reduced or preserved ejection fraction (LVEF ≥ 40%).[4] Treatment should not be initiated in patients with serum or plasma potassium levels greater than 5.0 mmol/L (i.e., severe hyperkalemia) or with an eGFR less than 25 mL/min/1.73 m^2.[4]

Canada's Drug Agency: Vericiguat Reimbursement Recommendation (2023)
One phase 3, multicenter, double-blind, randomized placebo-controlled trial (VICTORIA; n=5,050) demonstrated that treatment with vericiguat when added to dual or triple background heart failure therapy resulted in added clinical benefit for patients with symptomatic chronic HFrEF who are stabilized after a recent heart failure decompensation event.[5] In the VICTORIA trial, background therapy included beta blockers; ACE inhibitors, ARBs, or an ARNI; and MRA.[5] In the VICTORIA trial, 91.4% of patients were receiving at least 2 medications, 60% of patients were receiving 3 medications, and 14% of patients were receiving sacubitril-valsartan as one of the medications.[5] No patients received background therapy with SGLT2 inhibitors in the VICTORIA trial; therefore, the cumulative benefit and potential harms of adding vericiguat to standard quadruple therapy or adding vericiguat instead of SGLT2 inhibitors to triple therapy remains unknown.[5] There was no evidence from the VICTORIA trial that demonstrated whether patients who are intolerant to one or more of the classes of medications included in standard heart failure therapy may benefit from the addition of vericiguat.[5] Compared with placebo, treatment with vericiguat was associated with a statistically significant and clinically meaningful reduction in the hazard of a first event of CV death or hospitalization for heart failure (hazard ratio [HR] = 0.90; 95% CI, 0.82 to 0.98).[5] Compared to placebo, the hazard of the first event of all-cause mortality or hospitalization for heart failure was lower in the vericiguat group (HR = 0.90; 95% CI, 0.83 to 0.98).[5]

- Canada's Drug Agency recommends that vericiguat be reimbursed for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent heart failure decompensation event requiring hospitalization and/or IV diuretic therapy.[5]

National Institute for Health and Care Excellence (NICE): Management of Chronic Heart Failure in Adults (2025)
Recommendations for treating HFrEF, HFmrEF, and HFpEF were revised in the updated NICE guidance for management of adults with chronic heart failure.[6]
<u>Management of people with HFrEF:</u>

- Offer an ACE inhibitor, beta-blocker, MRA, and SGLT2 inhibitor to people with HFrEF.[6]
- For people on maximum tolerated dose of the each of the 4 recommended medicines who continue to have symptoms of HFrEF, consider switching the ACE inhibitor to an ARNi.[6]
- For people with HFrEF who have angioedema after taking an ACE inhibitor, or who have symptoms of intolerance to ARNis, consider an ARB in addition to a beta blocker, MRA, and SGLT2 inhibitor.[6]
- For people with HFrEF who have symptoms of intolerance to ACE inhibitors (other than angioedema), offer an ARNi, a beta blocker, MRA, and SGLT2 inhibitor.[6]
- If ACE inhibitors, ARNis, and ARBs are not tolerated, consider hydralazine in combination with nitrate.[6]
- Offer digoxin to people with worsening or severe HFrEF despite optimized GDMT.[6]
- Avoid verapamil, diltiazem, and short-acting dihydropyridine agents in people with HFrEF.[6]

Management of people with HFmrEF:

- Consider an ACE inhibitor, beta-blocker, MRA, and SGLT2 inhibitor to people with HFmrEF.[6]
- For people with HFmrEF who have symptoms of intolerance to ACE inhibitors, consider an ARB, beta blocker, MRA, and SGLT2 inhibitor (empagliflozin or dapagliflozin).[6]

Management of people with HFpEF:

- Consider an MRA and SGLT2 inhibitor (empagliflozin or dapagliflozin) for treating HFpEF.[6]

Update of European Society of Cardiology: Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2023)

This focused guidance was developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the ESC.[7] Interim focused updates are created when the publication of new evidence could influence clinical practice before the next full update of a guideline is published.[7] Classes of recommendations (COR) and levels of evidence (LOE) are described below.

Classes of Recommendations[7]

- Class I: There is evidence and/or general agreement that a given procedure or treatment is effective and/or useful
- Class IIa: There is a high probability of efficacy/usefulness based on evidence and opinion
- Class IIb: Effectiveness/usefulness is not well established based on evidence and opinion
- Class III: No Benefit: There is evidence or general agreement that the procedure or treatment is not effective and/or useful
- Class III: Harm: There is evidence and/or general agreement that the procedure or treatment is harmful

Levels of Evidence[7]

- Level A: Demonstrated by multiple high-quality RCTs or meta-analyses
- Level B-R: Demonstrated by 1 or more RCTs
- Level B-NR: Demonstrated by 1 or more well-designed, well-executed non-randomized, observational, or registry studies
- Level C-LD: Demonstrated by randomized or non-randomized, observational, or registry studies with design or methodological limitations
- Level C-EO: Consensus of expert opinion based on clinical experience

- Recommendation for the treatment of patients with symptomatic HFmrEF:
  - An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of heart failure hospitalization or CV death (COR: I; LOE: A).[7]
- Recommendation for the treatment of patients with symptomatic HFpEF:
  - An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of heart failure hospitalization or CV death (COR: I; LOE: A).[7]
- Recommendations for the prevention of heart failure in patients T2DM and CKD:
  - In patients with T2DM and CKD, SGLT2 inhibitors are recommended to reduce the risk of heart failure hospitalization and CV death (COR: I; LOE: A).[7]
  - In patients with T2DM and CKD, finerenone is recommended to reduce the risk of heart failure hospitalization (COR: I; LOE: A).[7]

American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) Guideline for the Management of Heart Failure (2022)

The 2022 ACC/AHA/HFSA guideline consolidated 2013 and 2017 recommendations into a new document along with recently published evidence for new treatment strategies.[8] In the U.S., approximately 115 million people have hypertension, 100 million have obesity, 92 million have prediabetes, 26 million have diabetes, and 125 million have atherosclerotic CVD.[8] These are known risk factors with high relative risk and population attributable risk for development of heart failure.[8] Therefore, a large proportion of the U.S. population can be categorized as being at-risk for heart failure (stage A).[8] The common causes of heart failure include ischemic heart disease and MI, hypertension, and valvular heart disease (VHD).[8] Stage B or pre-heart failure, represents a phase of clinically asymptomatic structural and functional cardiac abnormalities that increases the risk for symptomatic heart failure.[8] Stages of heart failure were revised in the 2022 guidance to emphasize the new terminologies of at risk for heart failure (Stage A) and pre-heart failure (Stage B.)[8] Classes of recommendations (COR) and levels of evidence (LOE) are defined in the ESC guidance above.

- Pharmacologic recommendations for patients at risk of heart failure (Stage A) include:
    - In patients with hypertension, blood pressure should be controlled in accordance with GDMT for hypertension to prevent symptomatic heart failure (COR: I; LOE: A).[8]
    - In patients with T2DM and either established CVD or at high cardiovascular risk, SGLT2 inhibitors should be used to prevent hospitalizations for heart failure (COR: I; LOE: A).[8]

- Pharmacologic recommendations for patients in pre-heart failure (Stage B) include:
    - In patients with LVEF < 40%, ACE inhibitors should be used to prevent symptomatic heart failure and reduce mortality (COR: I; LOE: A).[8]
    - In patients with a recent or remote history of MI or acute coronary syndrome (ACS), statins should be used to prevent symptomatic heart failure and adverse CV events (COR: I; LOE: A).[8]
    - In patients with a recent MI and LVEF ≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic heart failure and reduce mortality (COR: I; LOE: B-R).[8]
    - In patients with a recent or remote history of MI or ACS and LVEF ≤ 40%, evidence-based beta blockers should be used to reduce mortality (COR: I; LOE: B-R).[8]
    - In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic heart failure (COR: I; LOE: C-LD).[8]
    - In patients with LVEF <50%, thiazolidinediones should not be used because they increase the risk of heart failure, including hospitalization (COE: 3-Harm; LOE: B-R).[8]
    - In patients with LVEF <50%, non-dihydropyridine calcium channel blockers with negative inotropic effects may be harmful (COE: 3-Harm; LOE: LD).[8]

Loop diuretics (bumetanide, furosemide, torsemide) are the preferred diuretic agents for use in most patients with heart failure.[8] Thiazide diuretics such as chlorthalidone or hydrochlorothiazide may be considered in patients with hypertension and heart failure and mild fluid retention.[8] Metolazone or chlorothiazide may be added to loop diuretics in patients with refractory edema unresponsive to loop diuretics alone.[8] The treatment goal of diuretic use is to eliminate clinical evidence of fluid retention, using the lowest dose possible to maintain euvolemia.[8] With the exception of MRAs, the effects of diuretics on morbidity and mortality are uncertain.[8] As such, diuretics should not be used in isolation but always combined with other GDMT for heart failure that reduces hospitalizations and prolongs survival.[8]

Recommendations for diuretics and decongestion strategies in patients with heart failure include:

- In patients with heart failure who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening heart failure (COR: I; LOE: B-NR).[8]
- For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate- or high-dose loop diuretics to minimize electrolyte abnormalities (COR: I; LOE: B-NR).[8]

Heart Failure Classification by LVEF[8]

- HFrEF is defined as LVEF ≤ 40%.
- Heart failure with an LVEF of between 41% and 49% is classified as HFmrEF.
- HFpEF is defined as LVEF ≥ 50%.
- HFimpEF is defined as HF in patients whose initial LVEF was ≤ 40%, with a subsequent increase in LVEF ≥ 10% and a resulting LVEF greater than 40% based on longitudinal assessment.

Pharmacologic recommendations for management of HFrEF, HFmrEF, and HFpEF are presented in **Table 1, 2**, and **3,** respectively.
Recent changes include:

- Guideline-directed medical therapy for HFrEF includes the following 4 medication classes: RAAS/ARNIs, beta blockers, MRAs, and SGLT2 inhibitors.[8]
- SGLT2 inhibitors are recommended in HFmrEF (COR: IIa). Weaker recommendations are made for ARNi, ACE inhibitor, ARB, MRA, and beta blockers for patients with HFmrEF.[8]
- New recommendations for HFpEF are made for SGLT2 inhibitors (COR: IIa), MRAs (COR: IIb), and ARNi (COR: IIb).[8]
- Improved LVEF is used to refer to those patients with previous HFrEF who now have an LVEF > 40%. These patients should continue their HFrEF treatment.[8]

Table 1. Pharmacotherapy Recommendations for Heart Failure with Reduced Ejection Fraction[8]

Recommendation	COR	LOE
In patients with HFrEF and NYHA class II–III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.	I	A
In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNi is not feasible.	I	A
In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACE inhibitor because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality.	I	A
In patients with chronic symptomatic HFrEF, NYHA class II or III, who tolerate an ACE inhibitor or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality.	I	B-R
An ARNi should not be administered concomitantly with an ACE inhibitor or within 36 hours of the last dose of an ACE inhibitor.	III Harm	B-R
ARNi or ACE inhibitor should not be administered to patients with any history of angioedema.	III Harm	C-LD
In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalization	I	A

In patients with HFrEF and NYHA class II-IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if estimated glomerular filtration rate is > 30 mL/min/1.73 m2 and serum potassium is < 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency.	I	A
In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia.	III Harm	B-R
In patients with symptomatic chronic HFrEF, an SGLT2 inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.	I	A
For patients self-identified as African American with NYHA class III–IV HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality.	I	A
In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality.	IIb	C-LD
In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid (PUFA) supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations.	IIb	B-R
In patients with chronic HFrEF without a specific indication (e.g., venous thromboembolism, AF, a previous thromboembolic event, or a cardioembolic source), anticoagulation is not recommended.	3 No Benefit	B-R
For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥70 bpm at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death.	IIa	B-R
In patients with symptomatic HFrEF despite GDMT (or who are unable to tolerate GDMT), digoxin might be considered to decrease hospitalizations for HF.	IIb	B-R
In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death.	IIb	B-R
Abbreviations: ACEi = Angiotensin-Converting Enzyme Inhibitor; ARBs = Angiotensin Receptor Blockers; ARNi = Angiotensin Receptor-Neprilysin Inhibitor; COR = Class Of Recommendation; GDMT = Guideline-Directed Medical Therapy; HF = Heart Failure; HFrEF = Heart Failure With Reduced Ejection Fraction; LOE = Level Of Evidence; MRA = Mineralocorticoid Receptor Antagonists; NYHA = New York Heart Association; SGLT2 = Sodium-Glucose Cotransporter 2		

Table 2. Pharmacotherapy Recommendations for HF with Mildly Reduced Ejection Fraction[8]

Recommendation	COR	LOE
In patients with HFmrEF, SGLT2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.	IIa	B-R
In patients with current or previous symptomatic HFmrEF (LVEF, 41%–49%), use of evidence-based beta-blockers for HFrEF, ARNi, ACE inhibitor or ARB, and MRAs may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum.	IIb	B-NR
Abbreviations: ACEi = Angiotensin-Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; ARNi = Angiotensin Receptor-Neprilysin Inhibitor; COR = Class of Recommendation; HF = Heart Failure; HFmrEF = Heart Failure with Mildly Reduced Ejection Fraction; LOE = Level of Evidence; LVEF = left ventricular ejection fraction; MRAs = Mineralocorticoid Receptor Antagonists; SGLT2 = Sodium-Glucose Cotransporter 2		

Table 3. Pharmacotherapy Recommendations for HF with Preserved Ejection Fraction[8]

Recommendation	COR	LOE
In patients with HFpEF, SGLT2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.	IIa	B-R
In selected patients with HFpEF, MRA may be considered to decrease hospitalizations, particularly in patients with LVEF on the lower end of the spectrum.	IIb	B-R
In selected patients with HFpEF, ARNis may be considered to decrease hospitalizations, particularly in patients with LVEF on the lower end of this spectrum.	I	C-LD
In patients with HFpEF, management of AF can be useful to improve symptoms.	IIa	C-EO
In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly in patients with LVEF on the lower end of this spectrum	IIb	B-R
In patients with HFpEF, routine use of nitrates of phosphodiesterase-5 inhibitors to increase activity or quality of life is ineffective.	3 No Benefit	B-R

Abbreviations: ARB = Angiotensin Receptor Blocker; AF = atrial fibrillation; ARNis = Angiotensin Receptor-Neprilysin Inhibitors; COR = Class of Recommendation; HF = Heart Failure; HFpEF = Heart Failure with Preserved Ejection Fraction; LOE = Level of Evidence; LVEF = left ventricular ejection fraction; MRA = Mineralocorticoid Receptor Antagonist; SGLT2 = Sodium-Glucose Cotransporter 2

After review, 2 guidelines were excluded due to poor quality.[18,19]

New Formulations and Indications:

New Formulations

- 10/2025: The FDA approved LASIX ONYU, a single-use, subcutaneous injection form of furosemide designed to administer 80 mg over 5 hours.[9] The single-use, prefilled cartridge contains furosemide 80 mg/2.67 mL.[9] The infuser device delivers furosemide 30 mg over the first hour, then 12.5 mg per hour for the subsequent 4 hours.[9] LASIX ONYU is indicated for the treatment of edema in adult patients with heart failure.[9] The FDA based the approval of LASIX ONYU on pharmacokinetic studies that showed subcutaneous administration of LASIX ONYU produced similar diuresis and natriuresis to IV furosemide administration at 8- and 24-hours post-dose in patients with edema due to heart failure.[9]

- 9/2025: The FDA approved ENBUMYST, a new dosage form of bumetanide nasal spray which contains 0.5 mg/0.1 mL per each unit of use device.[10] ENBUMYST indicated for the treatment of edema associated with congestive heart failure, hepatic cirrhosis, and renal disease, including nephrotic syndrome in adults.[10] The usual total daily dose of bumetanide is 0.5 mg to 2 mg once daily; the number of nasal spray devices needed for a single dose depends on the prescribed dose.[10] The nasal spray is not intended for chronic use, it should be replaced with oral diuretics as soon as practical.[10] The FDA based the approval of ENBYMYST on clinical trials that supported the safety and efficacy of oral bumetanide.[10] Pharmacokinetic studies demonstrated the bioequivalency of bumetanide nasal spray to oral and IV bumetanide formulations.[10]

- 7/2025: The FDA approved VOSTALLY a new dosage form of ramipril oral suspension 1 mg/mL, indicated for the treatment of hypertension in adults; to reduce the risk of MI, stroke or death from CV causes in patients 55 years or older at high risk of developing major CV events; and to reduce the risk of CV death and hospitalization for heart failure in adults with post-MI heart failure.[11] The FDA approval was based on pharmacokinetic studies demonstrating the bioequivalency of the oral suspension to oral forms of ramipril tablets and capsules.[11]

- 3/2025: The FDA approved ARBLI, a new dosage form of losartan oral suspension 10 mg/mL, indicated for the treatment of hypertension in adults and children greater than 6 years old; reduction of stroke in patients with hypertension and left ventricular hypertrophy (there is evidence that this benefit does not apply to Black patients); and treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with T2DM and a history of hypertension.[12] The FDA based the approval of ARBLI on clinical trials that supported the safety and efficacy of losartan tablets.[10] Pharmacokinetic studies demonstrated the bioequivalency of losartan oral suspension to oral losartan tablet formulations.[10]

- 3/2025: The FDA approved HEMICLOR, a new oral dosage form of chlorthalidone 12.5 mg tablets indicated for the treatment of hypertension in adults.[13] The manufacturer did not conduct any clinical studies for this dosage form, instead a literature-based review was submitted to the FDA to support the efficacy of 12.5 mg dosing of chlorthalidone to control hypertension alone or in combination with other antihypertensive medications.[13]

- 1/2025: The FDA approved INZIRQO, a new dosage form of hydrochlorothiazide oral suspension 10 mg/mL, indicated for the treatment of hypertension in adults and pediatric patients and for the treatment of edema associated with congestive heart failure, hepatic cirrhosis, and renal disease in adults and pediatrics.[14] The approval was based on pharmacokinetic studies comparing the oral suspension to oral forms of generic hydrochlorothiazide tablets. Previous findings from published safety and efficacy studies for hydrochlorothiazide tablets also supported the FDA approval.[14]

- 10/2022: The FDA approved FUROSCIX, a single-use, subcutaneous injection form of furosemide designed to administer 80 mg over 5 hours.[15] The prefilled cartridge contains furosemide 80 mg/10 mL.[15] The on-body infuser device is a pre-programmed cartridge designed to deliver 30 mg of furosemide over the first hour, then 12.5 mg per hour for the subsequent 4 hours.[15] FUROSCIX is indicated for the treatment of congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure.[15] This indication was later expanded (see next section). This device is not for chronic use and should be replaced with oral diuretics as soon as practical.[15] The FDA based the approval of FUROSCIX on pharmacokinetic studies that showed subcutaneous administration of FUROSCIX produced similar diuresis and natriuresis to IV furosemide administration at 8- and 24-hours post-dose in patients with edema due to heart failure.[9]

New Indications:

- 12/2025: The FDA approved the expanded use of FUROSCIX for the treatment of edema in pediatric patients weighing 43 kg and above with chronic heart failure.[15] Previously, FUROSCIX was FDA-approved for treatment of edema in adults with chronic heart failure or chronic kidney disease.[7] (The CKD indication was added in March 2025). FUROSCIX has not been studied in pediatric patients.[15] Use of FUROSCIX for this indication is supported by: 1) efficacy, safety, and pharmacokinetic data of furosemide in adult and pediatric patients and 2) population pharmacokinetic modeling which demonstrated no significant difference in furosemide exposure following FUROSCIX administration in a simulated pediatric population weighing 43 kg and above and aged 6 to <17 years compared to adult patients with chronic heart failure.[15]

- 7/2025: The FDA approved an expanded indication of finerenone for reduction of risk of CV death, hospitalization for heart failure, and urgent heart failure visits in adults with heart failure and LVEF $\geq$ 40%.[16] The target daily dose of finerenone for heart failure (LVEF $\geq$ 40%) is dependent on renal function at initiation of treatment. The target dose is 40 mg once daily for eGFR $\geq$ 60 mL/min/1.73m^2 and 20 mg once daily if eGFR $\geq$ 25 to < 60 mL/min/1.73m^2.[16] Prior to this expanded indication, finerenone was approved to reduce the risk of sustained eGFR decline, end stage kidney disease, CV death, non-fatal MI and hospitalization for heart failure in adults with CKD associated with T2DM.[16] The target dose is this population is 20 mg once daily, based on eGFR and serum potassium thresholds.[16]

The safety and efficacy of finerenone in patients with heart failure was evaluated in a double-blind, placebo-controlled, multicenter RCT, FINEARTS-HF, in which a total of 3003 patients were treated with a target dose of 20 mg or 40 mg once daily of finerenone with a mean duration of treatment of 2.7 years.[16] The primary endpoint was the composite of CV death and total (first and recurrent) heart failure events comprised of hospitalization for heart failure and urgent heart failure visits.[16] Finerenone reduced the risk of the primary composite endpoint compared to placebo (RR 0.84; 95% CI 0.74 to 0.95; p = 0.007).[16] The overall safety profile of finerenone in the FINEARTS-HF study was largely consistent with the adverse reactions reported in patients with CKD and T2DM.[16]

- 4/2021: The FDA expanded the approval of valsartan to include children aged 1 year and older for the treatment of hypertension.[17] Previously, the treatment was indicated for patients 6 years of age and older with hypertension.[17] The antihypertensive effects of valsartan were evaluated in 3 single-arm clinical studies in pediatric patients from 1 to less than 6 years of age.[17] In all 3 RCTs, valsartan reduced systolic blood pressure.[17] The adverse experience profile of valsartan was similar to that described for adults.[17]

New FDA Safety Alerts:

Table 9. Description of New FDA Safety Alerts[20]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Spironolactone	CAROSPIR	8/2023	Use in Specific Populations	CAROSPIR is not recommended for the treatment of hypertension in pediatric patients because of the potential risks associated with the antiandrogenic, progestogenic, and estrogenic properties of spironolactone in pediatric patients.

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9. LASIX ONYU (furosemide) for subcutaneous injection. Prescribing Information. Burlington, MA; SQ Innovation, Inc. October 2025.
10. ENBUMYST (bumetanide) nasal spray. Prescribing Information. Henderson, NV; Corstasis Therapeutics. September 2025.
11. VOSTALLY (ramipril) oral solution. Prescribing Information. Watkinsville, GA; Metacel Pharmaceuticals, LLC. July 2025.
12. ARBLI (losartan potassium) oral suspension. Prescribing Information. Commack, NY; Scienture, LLC. February 2026.
13. HEMICLOR (chlorthalidone) oral tablets. Prescribing Information. Orlando, FL; Ingenus Pharmaceuticals, LLC. March 2025.
14. INZIRQO (hydrochlorothiazide) oral suspension. Prescribing Information. Baudette MN; ANI Pharmaceuticals, Inc. January 2025.
15. FUROSCIX (furosemide) subcutaneous injection. Prescribing Information. Burlington, MA; scPharmaceuticals, Inc. December 2025.
16. KERENDIA (finerenone) oral tablets. Prescribing Information. Whippany, NJ; Bayer HealthCare Pharmaceuticals, Inc. July 2025.
17. DIOVAN (valsartan) oral tablets. Prescribing Information. East Hanover, NJ; Novartis Pharmaceuticals Corportation. April 2021.
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Appendix 1: Current Preferred Drug List

Diuretics, oral

Generic	Brand	Route	Form	PDL
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	CAPSULE	Y
triamterene	TRIAMTERENE	ORAL	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	ORAL	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	ORAL	CAPSULE	Y
furosemide	FUROSEMIDE	ORAL	SOLUTION	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	SOLUTION	Y
spironolactone	ALDACTONE	ORAL	TABLET	Y
amiloride HCl	AMILORIDE HCL	ORAL	TABLET	Y
amiloride/hydrochlorothiazide	AMILORIDE HCL W/HCTZ	ORAL	TABLET	Y
amiloride/hydrochlorothiazide	AMILORIDE-HYDROCHLOROTHIAZIDE	ORAL	TABLET	Y
bumetanide	BUMETANIDE	ORAL	TABLET	Y
chlorthalidone	CHLORTHALIDONE	ORAL	TABLET	Y
furosemide	FUROSEMIDE	ORAL	TABLET	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	TABLET	Y
indapamide	INDAPAMIDE	ORAL	TABLET	Y
furosemide	LASIX	ORAL	TABLET	Y
spironolactone	SPIRONOLACTONE	ORAL	TABLET	Y
spironolact/hydrochlorothiazid	SPIRONOLACTONE-HCTZ	ORAL	TABLET	Y
torsemide	TORSEMIDE	ORAL	TABLET	Y
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	ORAL	TABLET	Y
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	ORAL	TABLET	Y
spironolactone	CAROSPIR	ORAL	ORAL SUSP	N
spironolactone	SPIRONOLACTONE	ORAL	ORAL SUSP	N
furosemide	FUROSEMIDE	ORAL	SOLUTION	N
hydrochlorothiazide	INZIRQO	ORAL	SUSP RECON	N
eplerenone	EPLERENONE	ORAL	TABLET	N
ethacrynic acid	ETHACRYNIC ACID	ORAL	TABLET	N
chlorthalidone	HEMICLOR	ORAL	TABLET	N
eplerenone	INSPRA	ORAL	TABLET	N
finerenone	KERENDIA	ORAL	TABLET	N
metolazone	METOLAZONE	ORAL	TABLET	N
chlorthalidone	THALITONE	ORAL	TABLET	N
metolazone	METOLAZONE	ORAL	TABLET	
hydroflumethiazide	SALURON	ORAL	TABLET	
furosemide	FUROSCIX	SUBCUT	KIT	

furosemide*	LASIX ONYU	SUBCUT	KIT	
bumetanide*	ENBUMYST	NASAL	SPRAY	

Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)

Generic	Brand	Route	Form	PDL
ramipril	RAMIPRIL	ORAL	CAPSULE	Y
quinapril HCl	ACCUPRIL	ORAL	TABLET	Y
candesartan cilexetil	ATACAND	ORAL	TABLET	Y
irbesartan	AVAPRO	ORAL	TABLET	Y
benazepril HCl	BENAZEPRIL HCL	ORAL	TABLET	Y
olmesartan medoxomil	BENICAR	ORAL	TABLET	Y
candesartan cilexetil	CANDESARTAN CILEXETIL	ORAL	TABLET	Y
losartan potassium	COZAAR	ORAL	TABLET	Y
valsartan	DIOVAN	ORAL	TABLET	Y
enalapril maleate	ENALAPRIL MALEATE	ORAL	TABLET	Y
fosinopril sodium	FOSINOPRIL SODIUM	ORAL	TABLET	Y
irbesartan	IRBESARTAN	ORAL	TABLET	Y
lisinopril	LISINOPRIL	ORAL	TABLET	Y
losartan potassium	LOSARTAN POTASSIUM	ORAL	TABLET	Y
benazepril HCl	LOTENSIN	ORAL	TABLET	Y
telmisartan	MICARDIS	ORAL	TABLET	Y
olmesartan medoxomil	OLMESARTAN MEDOXOMIL	ORAL	TABLET	Y
lisinopril	PRINIVIL	ORAL	TABLET	Y
quinapril HCl	QUINAPRIL HCL	ORAL	TABLET	Y
telmisartan	TELMISARTAN	ORAL	TABLET	Y
valsartan	VALSARTAN	ORAL	TABLET	Y
lisinopril	ZESTRIL	ORAL	TABLET	Y
losartan potassium	ARBLI	ORAL	ORAL SUSP	N
sacubitril/valsartan	ENTRESTO SPRINKLE	ORAL	PEL DSP CP	N
enalapril maleate	ENALAPRIL MALEATE	ORAL	SOLUTION	N
enalapril maleate	EPANED	ORAL	SOLUTION	N
lisinopril	QBRELIS	ORAL	SOLUTION	N
aliskiren hemifumarate	ALISKIREN	ORAL	TABLET	N
captopril	CAPTOPRIL	ORAL	TABLET	N
azilsartan medoxomil	EDARBI	ORAL	TABLET	N
sacubitril/valsartan	ENTRESTO	ORAL	TABLET	N
moexipril HCl	MOEXIPRIL HCL	ORAL	TABLET	N
perindopril erbumine	PERINDOPRIL ERBUMINE	ORAL	TABLET	N

sacubitril/valsartan	SACUBITRIL-VALSARTAN	ORAL	TABLET	N
aliskiren hemifumarate	TEKTURNA	ORAL	TABLET	N
eprosartan mesylate	TEVETEN	ORAL	TABLET	N
trandolapril	TRANDOLAPRIL	ORAL	TABLET	N
valsartan	VALSARTAN	ORAL	SOLUTION	
lisinopril	LISINOPRIL	ORAL	TABLET	

Vasodilators: Coronary

Generic	Brand	Route	Form	PDL
vericiguat	VERQUVO	PO	TABLET	N

*Not currently a rebatable product

Appendix 2: New Comparative Clinical Trials

A total of 165 citations were manually reviewed from the initial literature search. After further review, 135 citations were excluded because of wrong study design (e.g., observational), comparator (ego, no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Mentz, RJ, et al[21] OL, RCT	1. Oral torsemide: dosing determined by provider N=1431 Vs. 2. Oral furosemide: dosing determined by provider N=1428 Dosing conversion guide: Torsemide 1 mg to Furosemide 2-4 mg	Inclusion Criteria: Patients over 18 yo with LVEF ≤ 40% within 24 mos Or Elevated BNP (baseline not described) Exclusions: -CKD requiring dialysis -History of heart transplant or LVAD Demographics: Median age: 65 yo Female: 37% Black: 34% Beta-blocker use: 82% RAAS use: 68% MRA use: 44% SGLT2i use: 8%	All-cause mortality in a time-to-event analysis over 30 months after discharge for HF exacerbation	All-cause mortality rates over 17.4 mos: 1. 373 (26.1%) 2. 374 (26.2%) HR: 1.02 95% CI 0.89 to 1.18 P= 0.76 Among patients discharged after hospitalization for heart failure, torsemide compared with furosemide did not result in a significant difference in all-cause mortality over 12 months.	-Nonadherence at 30 days was 7% and at 6 mos was 9.5% of patients -7% crossover from torsemide to furosemide and 3.85% crossover from furosemide to torsemide -Variations in baseline GDMT among enrolled patients -Dosing discretion led to variations in how each diuretic was prescribed -Interpretation of these findings is limited by loss to follow-up, participant crossover to different diuretic therapy, and nonadherence to diuretic therapy
Pieske B, et al[22] PARALLAX RCT DB, AC/PC, RCT	1. Sacubitril/valsartan 97 mg/103 mg twice daily N=1281 Vs. 2. RAAS therapy (enalapril 10 mg,	Inclusion Criteria: -Patients 45 yo and older with HF and LVEF > 40% requiring diuretic treatment -NYHA Class II-IV -Plasma NT-proBNP > 220 pg/mL in NSR and > 600 pg/mL for	Co-primary end points were change from baseline in plasma NT-proBNP level at week 12 and in the 6-minute walk distance at week 24.	1. Change from baseline in NT-proBNP after 12 weeks Median baseline NT-proBNP = 786 pg/mL in the sacubitril/valsartan arm and 760 pg/mL in the comparator group. Median NT-proBNP at 12 weeks not reported for either arm.	--NT-proBNP is a prognostic biomarker in HF, surrogate endpoint -A clinically significant decrease in NT-proBNP is a drop of 25-30% -Results reported as change in geometric mean ratio which indicates a shift in the average rate of decline -Short trial duration (24 weeks)

	valsartan 160 mg, or placebo) N=1285 Enalapril: n = 510 Valsartan: n = 558 Placebo: n= 148 Trial Duration: 24 weeks 396 centers in 32 countries	patients with AF or atrial flutter -Structural heart disease (left atrial enlargement or left ventricular hypertrophy) -If on ACEi/ARB therapy, must have history of HTN Exclusions: -LVEF $\leq$ 40% -Acute coronary syndrome, cardiac surgery -Acute decompensated HF within 30 days of study entry -SBP $\geq$ 180 -Serum potassium > 5.2 mmol/L Demographics: -Mean age: 72.6 yo -Female: 51% -Baseline median NT-proBNP: 786 pg/mL (sacubitril/valsartan) vs. 760 pg/mL (RAAS)		Results reported as adjusted mean geometric ratio, where a ratio lower than 1 favors sacubitril/valsartan 1. Adjusted mean ratio to baseline: 0.82 pg/mL 2. Adjusted mean ratio to baseline: 0.98 pg/mL Adjusted geometric mean ratio: 0.84 95% CI 0.80 to 0.88 P<0.0001 2. Change from baseline in exercise capacity as assessed by the 6MWT at 24 weeks 1. Increased by 9.7 meters 2. Increased by 12.2 meters Mean Difference: -2.5 meters 95% CI -8.5 to 3.5 meters P=0.42 Compared with standard medical therapies, sacubitril/valsartan resulted in a significantly greater decrease in plasma N-terminal pro–brain natriuretic peptide at 12 weeks but did not improve submaximal exercise capacity at 24 weeks. The clinical significance of this change is not clear. Further research is needed to evaluate potential benefits of sacubitril/valsartan.	-Did not evaluate long term outcomes such as heart failure hospitalization or cardiovascular mortality
Abbreviations: 6MWT = 6 minute walk test; AC = active comparator; ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; CI = confidence interval; CKD = chronic kidney disease; DB = double-blind; GDMT = Guideline Directed Medical Therapy; GFR = glomerular filtration rate; HF = heart failure; HR = hazard ratio; HTN = hypertension; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; mg = milligrams; mos = months; mL = milliliters; MRA = mineralocorticoid receptor antagonist; NSR = normal sinus rhythm; NT-proBNP = N-terminal pro b-type natriuretic peptide; OL = open-label; PC = placebo controlled; pg = picogram; RAAS = renin-angiotensin-aldosterone system; SGLT2i = sodium glucose transporter 2 inhibitor; RAAS = RCT = randomized clinical trial; SBP = systolic blood pressure; Scr = serum creatinine; yo = years old				

Appendix 3: Abstracts of Comparative Clinical Trials

***Effect of Torsemide vs Furosemide After Discharge on All-Cause Mortality in Patients Hospitalized With Heart Failure: The TRANSFORM-HF Randomized Clinical Trial*[21]**

Objective: To determine whether torsemide results in decreased mortality compared with furosemide among patients hospitalized for heart failure.

Design, Setting, and Participants: TRANSFORM-HF was an open-label, pragmatic randomized trial that recruited 2859 participants hospitalized with heart failure (regardless of ejection fraction) at 60 hospitals in the United States. Recruitment occurred from June 2018 through March 2022, with follow-up through 30 months for death and 12 months for hospitalizations. The final date for follow-up data collection was July 2022.

Interventions: Loop diuretic strategy of torsemide (n = 1431) or furosemide (n = 1428) with investigator-selected dosage.

Main Outcomes and Measures: The primary outcome was all-cause mortality in a time-to-event analysis. There were 5 secondary outcomes with all-cause mortality or all-cause hospitalization and total hospitalizations assessed over 12 months being highest in the hierarchy. The prespecified primary hypothesis was that torsemide would reduce all-cause mortality by 20% compared with furosemide.

Results: TRANSFORM-HF randomized 2859 participants with a median age of 65 years (IQR, 56-75), 36.9% were women, and 33.9% were Black. Over a median follow-up of 17.4 months, a total of 113 patients (53 [3.7%] in the torsemide group and 60 [4.2%] in the furosemide group) withdrew consent from the trial prior to completion. Death occurred in 373 of 1431 patients (26.1%) in the torsemide group and 374 of 1428 patients (26.2%) in the furosemide group (hazard ratio, 1.02 [95% CI, 0.89-1.18]). Over 12 months following randomization, all-cause mortality or all-cause hospitalization occurred in 677 patients (47.3%) in the torsemide group and 704 patients (49.3%) in the furosemide group (hazard ratio, 0.92 [95% CI, 0.83-1.02]). There were 940 total hospitalizations among 536 participants in the torsemide group and 987 total hospitalizations among 577 participants in the furosemide group (rate ratio, 0.94 [95% CI, 0.84-1.07]). Results were similar across prespecified subgroups, including among patients with reduced, mildly reduced, or preserved ejection fraction.

Conclusions and Relevance: Among patients discharged after hospitalization for heart failure, torsemide compared with furosemide did not result in a significant difference in all-cause mortality over 12 months. However, interpretation of these findings is limited by loss to follow-up and participant crossover and nonadherence.

***Effect of Sacubitril/Valsartan vs Standard Medical Therapies on Plasma NT-proBNP Concentration and Submaximal Exercise Capacity in Patients With Heart Failure and Preserved Ejection Fraction: The PARALLAX Randomized Clinical Trial*[22]**

Objective: To evaluate the effect of sacubitril/valsartan on N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, 6-minute walk distance, and quality of life vs background medication–based individualized comparators in patients with chronic heart failure and LVEF of more than 40%.

Design, Setting, and Participants: A 24-week, randomized, double-blind, parallel group clinical trial (August 2017-October 2019). Of 4632 patients screened at 396 centers in 32 countries, 2572 patients with heart failure, LVEF of more than 40%, elevated NT-proBNP levels, structural heart disease, and reduced quality of life were enrolled (last follow-up, October 28, 2019).

Interventions: Patients were randomized 1:1 either to sacubitril/valsartan (n = 1286) or to background medication–based individualized comparator (n = 1286), i.e., enalapril, valsartan, or placebo stratified by prior use of a renin angiotensin system inhibitor.

Main Outcomes and Measures: Primary end points were change from baseline in plasma NT-proBNP level at week 12 and in the 6-minute walk distance at week 24. Secondary end points were change from baseline in quality-of-life measures and New York Heart Association (NYHA) class at 24 weeks.

Results: Among 2572 randomized patients (mean age, 72.6 years [SD, 8.5 years]; 1301 women [50.7%]), 2240 (87.1%) completed the trial. At baseline, the median NT-proBNP levels were 786 pg/mL in the sacubitril/valsartan group and 760 pg/mL in the comparator group. After 12 weeks, patients in the sacubitril/valsartan group (adjusted geometric mean ratio to baseline, 0.82 pg/mL) had a significantly greater reduction in NT-proBNP levels than did those in the comparator group (adjusted geometric mean ratio to baseline, 0.98 pg/mL) with an adjusted geometric mean ratio of 0.84 (95% CI, 0.80 to 0.88; P < .001). At

week 24, there was no significant between-group difference in median change from baseline in the 6-minute walk distance with an increase of 9.7 m vs 12.2 m (adjusted mean difference, −2.5 m; 95% CI, −8.5 to 3.5; P = .42). There was no significant between-group difference in the mean change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (12.3 vs 11.8; mean difference, 0.52; 95% CI, −0.93 to 1.97) or improvement in NYHA class (23.6% vs 24.0% of patients; adjusted odds ratio, 0.98; 95% CI, 0.81 to 1.18). The most frequent adverse events in the sacubitril/valsartan group vs the comparator group were hypotension (14.1% vs 5.5%), albuminuria (12.3% vs 7.6%), and hyperkalemia (11.6% vs 10.9%)

Conclusions and Relevance: Among patients with heart failure and left ventricular ejection factor of higher than 40%, sacubitril/valsartan treatment compared with standard renin angiotensin system inhibitor treatment or placebo resulted in a significantly greater decrease in plasma N-terminal pro–brain natriuretic peptide levels at 12 weeks but did not significantly improve 6-minute walk distance at 24 weeks. Further research is warranted to evaluate potential clinical benefits of sacubitril/valsartan in these patients.

Appendix 4: Medline Search Strategy

DIURETICS

Ovid MEDLINE(R) ALL <1946 to April 01, 2026>

1	Hydrochlorothiazide/tu [Therapeutic Use]	3266
2	Triamterene/ or Diuretics/	31072
3	exp Furosemide/tu [Therapeutic Use]	3952
4	exp Spironolactone/tu [Therapeutic Use]	3503
5	Amiloride/tu [Therapeutic Use]	660
6	exp Bumetanide/tu [Therapeutic Use]	272
7	exp Chlorthalidone/tu [Therapeutic Use]	885
8	exp Indapamide/tu [Therapeutic Use]	615
9	exp Torsemide/tu [Therapeutic Use]	40
10	exp Eplerenone/tu [Therapeutic Use]	148
11	exp Ethacrynic Acid/tu [Therapeutic Use]	408
12	Naphthyridines/ or finerenone.mp.	4956
13	exp Metolazone/tu [Therapeutic Use]	89
14	exp Hydroflumethiazide/tu [Therapeutic Use]	44
15	finerenone.mp. or Mineralocorticoid Receptor Antagonists/	7234
16	Diuretics, Potassium Sparing/ or Diuretics/ or Diuretics, Osmotic/	31303
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	49910
18	Heart Failure/th [Therapy]	32277
19	17 and 18	1246
20	limit 19 to (english language and humans and yr="2021 -Current")	142

Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)

Ovid MEDLINE(R) ALL <1946 to March 31, 2026>

1	exp Ramipril/tu [Therapeutic Use]	1118
2	exp Quinapril/	639
3	candesartan.mp. or Angiotensin II Type 1 Receptor Blockers/	11799
4	exp Irbesartan/tu [Therapeutic Use]	85
5	Angiotensin-Converting Enzyme Inhibitors/ or benazepril.mp.	37931
6	Olmesartan Medoxomil/tu [Therapeutic Use]	24
7	exp Losartan/tu [Therapeutic Use]	2355
8	exp Valsartan/tu [Therapeutic Use]	724
9	exp Enalapril/tu [Therapeutic Use]	3263

10	exp Fosinopril/tu [Therapeutic Use]	215
11	exp Lisinopril/tu [Therapeutic Use]	852
12	exp Telmisartan/tu [Therapeutic Use]	170
13	exp Enalapril/tu [Therapeutic Use]	3263
14	exp Captopril/tu [Therapeutic Use]	3946
15	azilsartan.mp.	354
16	moexipril.mp.	123
17	exp Perindopril/tu [Therapeutic Use]	849
18	eprosartan.mp.	439
19	trandolapril.mp.	752
20	aliskiren.mp.	1352
21	Valsartan/	4145
22	sacubitril.mp.	2716
23	Soluble Guanylyl Cyclase/ or vericiguat.mp.	1855
24	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	59413
25	Heart Failure/th [Therapy]	32277
26	24 and 25	819
27	limit 26 to (english language and humans and yr="2021 -Current")	123

Appendix 5: Key Inclusion Criteria

Population	Adults and Children with Heart Failure
Intervention	Diuretics, ACE inhibitors, ARBs, MRAs, ARNis, Vericiguat
Comparator	Other active comparators used to manage heart failure
Outcomes	Resolution of heart failure systems, reduction in heart failure hospitalizations and CV events
Timing	6 months to 1 year
Setting	Outpatient

Finerenone

Goal(s):
- Promote use of finerenone that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:
- 12 months

Requires PA:
Finerenone (Kerendia™)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code; go to #2	
2. Does the patient have a diagnosis of heart failure with LVEF ≥ 40%?	**Yes:** Go to #5	**No:** Go to #3
3. Is the patient 18 years or older with a diagnosis of type 2 diabetes?	**Yes:** Go to #4	**No:** Pass to RPh; deny for medical appropriateness
4. Does the patient have a diagnosis of chronic kidney disease?	**Yes:** Go to #5	**No:** Pass to RPh; deny for medical appropriateness.
5. Does the patient have a documented estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) < 25 ml/min **OR** require hemodialysis?	**Yes:** Pass to RPh; deny for medical appropriateness. Request eGFR if not provided	**No:** Document eGFR and go to #6 Recent eGFR: _____ Date:

Approval Criteria		
6. Is the patient currently on standard of care for heart failure including a maximally tolerated angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI) OR have a documented contraindication to these medications?	**Yes:** Go to #7	**No:** Pass to RPh; deny for medical appropriateness.
7. Is the patient's serum potassium ≤ 5.0 mEq/L?	**Yes:** Approve for up to 12 months Recent potassium:____ Date: _____	**No:** Pass to RPh; deny for medical appropriateness.

P&T / DUR Review: *8/26 (DM); 06/22 (MH)*
Implementation: *TBD; 7/1/22*

Sacubitril/Valsartan (Entresto™) RET(RE

Goal(s):
- Restrict use of sacubitril/valsartan in populations and at doses in which the drug has demonstrated efficacy.
- Encourage use of beta-blockers with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:
- 3 to 12 months

Requires PA:
- Sacubitril/valsartan (Entresto™)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Does the patient have chronic heart failure (New York Heart Association [NYHA] Class II-IV)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient 17 years of age or younger?	**Yes:** Go to #5	**No:** Go to # 7
5. Does the patient have left ventricular systolic dysfunction (ejection fraction less than 40% (LVEF ≤ 40%)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the medication prescribed by or in consultation by a cardiologist or heart failure provider?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny, medical appropriateness
7. Has the patient tolerated a minimum daily dose of an ACE-inhibitor or ARB listed in Table 1 for at least 30 days? *Note: ACE inhibitors must be discontinued at least 36 hours prior to initiation of sacubitril/valsartan*	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have heart failure with reduced ejection fraction less than 40% (LVEF ≤ 40%)?	**Yes:** Go to #9	**No:** Approve for 3 months *Note: Benefits of therapy are most clearly evident in patients with left ventricular ejection fraction below normal. Use judiciously with higher baseline ejection fraction*

Approval Criteria		
9. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at target doses and are recommended by heart failure guidelines.[1,2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	**Yes:** Go to #10	**No:** Pass to RPh. Deny, medical appropriateness
10. Is there evidence of adherence and tolerance to goal directed heart failure therapy (beta-blocker and ACE-I/ARB) through pharmacy claims/refill history and provider assessment?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny, medical appropriateness

Renewal Criteria		
1. Is the patient 18 years or older or at least 50 kg?	**Yes:** Go to #2	**No:** Go to #3
2. Is the patient currently taking sacubitril/valsartan at the target dose of 97/103 mg 2-times daily to a maximum dose as tolerated by the patient?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh and go to #4
3. Is the patient currently taking sacubitril/valsartan at the target dose in Table 2 or to a maximum dose as tolerated by the patient?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh and go to #4
4. What is the clinical reason the drug has not been titrated to the target dose?	Document rationale and approve for up to 90 days. Prior authorization required every 90 days until target dose achieved.	

Table 1. Minimum Daily Doses of ACE-inhibitors or ARBs Required.[1,2]

ACE-inhibitor	Angiotensin-2 Receptor Blocker (ARB)

Captopril	100 mg/day	Candesartan	16 mg/day
Enalapril	10 mg/day	Losartan	50 mg/day
Lisinopril	10 mg/day	Valsartan	160 mg/day
Ramipril	5 mg/day	Olmesartan	10 mg/day
Trandolapril	2 mg/day	Irbesartan	150 mg/day
Fosinopril	20 mg/day		

Abbreviations: BID = twice daily; QDay = once daily; mg = milligrams; TID = three times daily.

Notes:

- Patients must achieve a minimum daily dose of one of the drugs listed for at least 30 days to improve chances of tolerability to the target maintenance dose of sacubitril/valsartan 97/103 mg 2-times daily.[3]
- Valsartan formulated in sacubitril valsartan 97/103 mg 2-times daily is bioequivalent to valsartan 160 mg 2-times daily.[4]
- It is advised that patients previously on an ACE-inhibitor have a 36-hour washout period before initiation of sacubitril/valsartan to reduce risk of angioedema.[3,4]

Table 2: Target dose of sacubitril/valsartan in pediatric heart failure[4]

Population	Target Dose
Patients less than 40 kg	3.1 mg/kg twice daily
Patients at least 40 kg, less than 50 kg	72/78 mg twice daily
Patients at least 50 kg	97/103 mg twice daily

References:

1. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2017;136(6): e137-e161.
2. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Journal of Heart Failure. 2012; 14:803-869. doi:10.1093/eurjhf/hfs105.
3. McMurray J, Packer M, Desai A, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Eng J Med*. 2014; 371:993-1004. doi:10.1056/NEJMoa1409077.
4. ENTRESTO (sacubitril and valsartan) [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals, February 2021.

P&T / DUR Review: *8/26(DM); 6/21(MH); 05/17(DM), 09/15*
Implementation: *TBD; 7/1/21; 10/13/16; 10/1/15*

Vericiguat (Verquvo®)

Goal(s):

- Restrict use of vericiguat in populations and at doses in which the drug has demonstrated efficacy.
- Encourage use of beta-blockers and inhibitors of the renin-angiotensin-aldosterone system with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Vericiguat (Verquvo®)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3.	
3. Does the patient have symptomatic New York Heart Association (NYHA) Class II to IV chronic heart failure?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have reduced ejection fraction (< 45%) assessed within the previous 12 months?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have worsening heart failure defined as one of the following? a. History of previous heart failure hospitalization within the last 6 months b. Intravenous diuretic use within previous 3 months	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient currently being seen by a cardiologist or heart failure specialist for management of advanced disease?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient on an angiotensin system inhibitor at maximally tolerated dose, such as: a. Angiotensin converting enzyme inhibitor (ACE-I) b. Angiotensin receptor blocker (ARB) c. Angiotensin receptor-neprilysin inhibitor (ARNI)	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at target doses and are recommended by national and international heart failure guidelines.[1,2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	**Yes:** Go to #9	**No:** Pass to RPh. Deny, medical appropriateness
9. Is there evidence of adherence and tolerance to goal directed heart failure therapy (beta-blocker and angiotensin inhibitor) through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #10	**No:** Pass to RPh. Deny, medical appropriateness
10. Is the patient on long-acting nitrates such as isosorbide dinitrate, isosorbide 5-mononitrate, transdermal nitroglycerin, or other similar agents or phosphodiesterase-5 (PDE5) inhibitors (e.g. sildenafil, tadalafil)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Does the patient have stage 5 chronic kidney disease (eGFR < 15 ml/min or on hemodialysis/peritoneal dialysis)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. Is the patient of childbearing potential?	**Yes:** Go to #13	**No:** Approve for 6 months
13. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny, medical appropriateness

Renewal Criteria		
1. Has the patient developed symptomatic hypotension or syncope while on vericiguat?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #2
2. Has the patient experienced disease progression, defined as either worsening NYHA functional class or worsening signs and symptoms of heart failure requiring intensification of therapy?	**Yes:** Go to #3	**No:** Approve for 12 months
3. Is the patient currently being seen by a cardiologist or heart failure specialist for management of advanced disease?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

References:
1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239. doi: 10.1016/j.jacc.2013.05.019.
2. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Journal of Heart Failure. 2012;14:803-869. doi:10.1093/eurjhf/hfs105.

P&T / DUR Review: *8/26 (DM); 06/21 (MH)*
Implementation: *TBD; 7/1/21*