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Heart Failure Treatment at a Glance

The chart below delineates the role of medications and other interventions for **heart failure with reduced ($\leq 40\%$) ejection fraction (HFrEF)**. For more information on dosing and titration, see our chart, *Target Doses of Meds for Heart Failure*. Our toolbox, *Improving Heart Failure Care*, provides practical tips and resources to help **improve care** in your heart failure patients and **prevent readmissions**.

Chart information may differ from product labeling. Canadian HF guideline recommendations included if significantly different from US.

Drug, Drug Class, or Intervention	Use for...
First-Line	
ARNI (sacubitril/valsartan [Entresto])	<ul style="list-style-type: none"> • Patients with Class II to III HF symptoms, to reduce morbidity and mortality.¹ • Also consider for patients with prior or current symptoms and EF 41% to 49% (US).¹ <p>Comments:</p> <ul style="list-style-type: none"> ○ May start at same time as beta-blocker, aldosterone antagonist, and/or SGLT2 inhibitor, but individualize sequencing and titration based on symptoms, functional status, vitals, kidney function, electrolytes, comorbidities, and follow-up.¹ For tips on initiating therapy based on kidney function, see our toolbox, <i>Improving Heart Failure Care</i>. ○ Do not use with an ACEI or ARB, or within 36 hours of the last dose of an ACEI, or in patients with a history of angioedema.^{4,5} ○ Pivotal trial excluded patients with symptomatic hypotension, SBP <100 mm Hg, serum potassium >5.2 mEq (mmol)/L, or eGFR <30 mL/min/1.73m².⁶ ○ Prevents CV death or HF hospitalization in 1 in 21 patients treated for two years vs an ACEI, but also causes symptomatic hypotension in 1 in 21 patients [Evidence level A-1].⁶ ○ Efficacy in early post-MI patients is unknown.¹ ○ Dosed twice daily.^{4,5}
ACEI	<ul style="list-style-type: none"> • Alternative for patients in whom an ARNI can't be used, to reduce morbidity and mortality.¹ • Patients with HF or EF <40% post-MI (Canada).² <p>Comments:</p> <ul style="list-style-type: none"> ○ For patients already tolerating an ACEI, consider switching to an ARNI to further reduce morbidity and mortality.¹ (Canada: switch patients who remain symptomatic or who have a HF hospitalization.²) ○ Wait at least 36 hours after stopping the ACEI if switching to <i>Entresto</i>, to reduce the risk of angioedema.^{4,5}

Drug, Drug Class, or Intervention	Use for...
First-Line , continued	
ARB	<ul style="list-style-type: none"> • Alternative for patients who are intolerant to ACEI due to cough or angioedema, in whom an ARNI can't be used.¹ • Patients with HF or EF <40% post-MI, who are intolerant of ACEI (Canada).² <p>Comments:</p> <ul style="list-style-type: none"> ○ For patients already tolerating an ARB, consider switching to an ARNI to further reduce morbidity and mortality.^{1,2} (Canada: switch patients who remain symptomatic or who have a HF hospitalization.²)
Beta-Blocker	<ul style="list-style-type: none"> • Hemodynamically stable patients with symptoms or prior symptoms, to reduce hospitalizations and mortality.¹ • Also consider for patients with prior or current symptoms and EF 41% to 49% (US).¹ <p>Comments:</p> <ul style="list-style-type: none"> ○ May start beta-blocker at same time as ARNI (or ACEI, or ARB), aldosterone antagonist, and/or SGLT2 inhibitor, but individualize sequencing and titration based on symptoms, functional status, vitals, kidney function, electrolytes, comorbidities, and follow-up.¹ For tips on initiating therapy based on kidney function, see our toolbox, <i>Improving Heart Failure Care</i>. • Beta-blocker initiation is best tolerated when the patient is “dry.”¹³ • Start even if patient is asymptomatic, has improved with other therapies.¹ ○ Use an evidence-based beta-blocker (carvedilol, bisoprolol, metoprolol succinate [US only]).¹ ○ Canada: patients with class III or IV heart failure should have their beta-blocker started by a specialist.²
Aldosterone Antagonist (eplerenone or spironolactone)	<ul style="list-style-type: none"> • Patients with Class II to IV HF symptoms, to reduce hospitalization and mortality, in patients with eGFR >30 mL/min/1.73m² and potassium <5 mEq (mmol)/L.¹ (Canada: post-MI with EF ≤40% and HF symptoms or diabetes.²) • Also consider for patients with prior or current symptoms and EF 41% to 49% (US).¹ <p>Comments:</p> <ul style="list-style-type: none"> ○ May start at same time as ARNI (or ACEI, or ARB), beta-blocker, and/or SGLT2 inhibitor, but individualize sequencing and titration based on symptoms, functional status, vitals, kidney function, electrolytes, comorbidities, and follow-up.¹ For tips on initiating therapy based on kidney function, see our toolbox, <i>Improving Heart Failure Care</i>. ○ Stop if potassium cannot be kept <5.5 mEq (mmol)/L.¹

Drug, Drug Class, or Intervention	Use for...
First-Line , continued	
SGLT2 inhibitor	<ul style="list-style-type: none"> • For patients (with or without diabetes) with HF symptoms, to reduce HF hospitalization and CV mortality.¹ • Also consider for patients with prior or current symptoms and EF 41% to 49% (US).¹ <p>Comments:</p> <ul style="list-style-type: none"> ○ May start at same time as ARNI (or ACEI, or ARB), beta-blocker, and/or aldosterone antagonist, but individualize sequencing and titration based on symptoms, functional status, vitals, kidney function, electrolytes, comorbidities, and follow-up.¹ ○ Adding empagliflozin (<i>Jardiance</i>) to standard HF treatment in patients with class II to IV HF for ~16 months prevents hospitalization or CV death in ~1 in 14 patients with type 2 diabetes, or ~1 in 26 patients without diabetes. This was driven mostly by hospitalizations.¹¹ ○ Adding dapagliflozin (<i>Farxiga</i>) to standard HF treatment in patients with class II to IV HF for ~1.5 years may reduce the composite endpoint of worsening HF (hospitalization or urgent visit requiring intravenous HF therapy) or CV death (NNT = 21 [patients with and without diabetes], NNT ~18 [patients with diabetes], or NNT ~22 [patients without diabetes]).¹²
Diuretics	<ul style="list-style-type: none"> • Patients with fluid retention or a history of fluid retention, to improve symptoms and exercise tolerance.¹ <p>Comments:</p> <ul style="list-style-type: none"> ○ Loops preferred, but thiazides can be considered for patients with hypertension and mild fluid retention.¹ ○ Diuretic dosage increase may be needed during beta-blocker uptitration.² ○ See our chart, Loop Diuretic Use in Heart Failure, for dosing and more.
Education to facilitate HF self-care	<ul style="list-style-type: none"> • Patients with symptoms or prior symptoms, to improve quality of life, prevent hospitalization, reduce mortality.¹
Avoidance of excessive sodium	<ul style="list-style-type: none"> • All symptomatic patients, to reduce symptoms and improve diuretic response.^{1,14} <p>Comments:</p> <ul style="list-style-type: none"> ○ Limiting sodium to 2 to 3 grams daily, as for general cardiovascular health, is reasonable.^{1,14}
Exercise (regular physical activity or cardiac rehab)	<ul style="list-style-type: none"> • Symptomatic but clinically stable patients who are able, to improve function and quality of life.¹

Drug, Drug Class, or Intervention	Use for...
First-Line Alternatives or Add-ons for Select Patients	
Hydralazine and Isosorbide Dinitrate	<ul style="list-style-type: none"> • Patients of African ancestry with Class III or IV HF symptoms (Canada: advanced symptoms) who are symptomatic despite optimized therapy (e.g., as an add-on first-line therapies), to improve symptoms and to reduce morbidity and mortality.^{1,2} • Alternative for patients who cannot take an ACEI, ARB, or ARNI (e.g., due to side effects such as hyperkalemia, or kidney insufficiency).^{1,2} Consider referring such patients to a heart failure specialist. <p>Comments:</p> <ul style="list-style-type: none"> ○ Insufficient data on use with ARNI.¹
Ivabradine (<i>Corlanor</i> [US], <i>Lancora</i> [Canada])	<ul style="list-style-type: none"> • Patients with symptomatic Class II or III stable chronic HF with EF $\leq 35\%$, in sinus rhythm with resting heart rate of ≥ 70 beats per minute (Canada: >70 beats [or ≥ 77 beats, per product labeling]), in addition to maximally-tolerated guideline-directed therapy (above), including a beta-blocker at a maximally-tolerated dose, or who cannot take a beta-blocker, to reduce HF hospitalization and cardiovascular death (composite endpoint).^{1,2,7,8} <p>Comments:</p> <ul style="list-style-type: none"> ○ Reduces HF hospitalization in one in 25 patients vs placebo when added to standard therapy [Evidence level A-1].⁹ ○ Causes bradycardia in one in 13 patients and atrial fibrillation in one in 100 patients vs placebo.^{7,9}
Last-Line Add-ons	
Digoxin	<ul style="list-style-type: none"> • Patients with persistent HF symptoms (Canada: moderate to severe symptoms) despite optimized guideline-directed therapy (above), to decrease HF hospitalization.^{1,2} • Patients with A Fib who need additional rate control (Canada).² <p>Comments:</p> <ul style="list-style-type: none"> ○ No loading dose needed for HF.¹ ○ Consider starting with 0.125 mg every-other-day in patients with renal insufficiency, low lean body mass, or age over 70 years.¹ Doses over 0.25 mg per day rarely needed.¹ ○ Levels ≥ 1.2 ng/mL are associated with increased mortality.¹
Vericiguat (<i>Verquvo</i>)(US) (guanylate cyclase stimulator) <i>Continued...</i>	<ul style="list-style-type: none"> • “Niche” drug for patients with symptomatic HF and EF $< 45\%$ with worsening HF (HF hospitalization within the previous six months or need for outpatient IV diuretics within the previous three months), to reduce the risk of CV death or HF hospitalization.^{1,10} <p>Comments:</p> <ul style="list-style-type: none"> ○ Sixty percent of patients in the pivotal clinical trial were on a beta-blocker, aldosterone antagonist, and either an ACEI, ARB, or <i>Entresto</i>.³

Drug, Drug Class, or Intervention	Use for...
Vericiguat, continued	<ul style="list-style-type: none"> ○ Prevents the composite endpoint (but not individual components) of hospitalization and CV death in ~1 in 33 patients over about one year.^{3,10} ○ Use with a phosphodiesterase-5 inhibitor (e.g., sildenafil) is not recommended (hypotension concern).^{3,10}

Abbreviations: ACEI=angiotensin-converting enzyme inhibitor, ACS = acute coronary syndrome, ARB=angiotensin receptor blocker, ARNI=angiotensin receptor-neprilysin inhibitor, BNP=B-type natriuretic peptide, CV = cardiovascular, EF = ejection fraction, HF=heart failure, IV = intravenous, MI=myocardial infarction, SBP = systolic blood pressure; SGLT2 = sodium glucose cotransporter 2

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	<ol style="list-style-type: none"> 1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	<ol style="list-style-type: none"> 1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. <https://www.aafp.org/afp/2004/0201/p548.pdf>.]

References

1. Writing Committee Members, Heidenreich PA, Bozkurt B, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022 Mar 24:S0735-1097(21)08395-9. doi: 10.1016/j.jacc.2021.12.012.
2. McDonald M, Virani S, Chan M, et al. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. *Can J Cardiol*. 2021 Apr;37(4):531-546.
3. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2020 May 14;382(20):1883-1893.
4. Product information for Entresto. Novartis. East Hanover, NJ 07936. February 2021.
5. Product monograph for Entresto. Novartis Canada. Dorval, QC H9S 1A9. July 2021.
6. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014 Sep 11;371(11):993-1004.
7. Product information for Corlanor. Amgen, Inc. Thousand Oaks, CA 91320. August 2021.
8. Product monograph for Lancora. Servier Canada. Laval, QC H7V 4A7. May 2018.
9. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010 Sep 11;376(9744):875-85. [Erratum in: *Lancet*. 2010 Dec 11;376(9757):1988.]
10. Product information for Verquvo. Merck & Co. Whitehouse Station, NJ 08889. June 2021.
11. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020 Oct 8;383(15):1413-1424.
12. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019 Nov 21;381(21):1995-2008.
13. Shore S. 2021 Expert Decision Pathway for HFrEF Treatment Optimization. January 11, 2021. <https://www.acc.org/Latest-in-Cardiology/ten-points-to-remember/2021/01/2021/21/56/2021-Update-Expert-Consensus-for-HFrEF>. (Accessed April 9, 2022).
14. Canadian Cardiovascular Society. Is it heart failure and what should I do? 2021 update. <https://ccs.ca/app/uploads/2021/04/2021-HF-Gui-PG-FINAL-WEB.pdf>. (Accessed April 8, 2022).

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