Circulation

AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

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

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AIM: The "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure" replaces the "2013 ACCF/AHA Guideline for the Management of Heart Failure" and the "2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure." The 2022 guideline is intended to provide patient-centric recommendations for clinicians to prevent, diagnose, and manage patients with heart failure.

METHODS: A comprehensive literature search was conducted from May 2020 to December 2020, encompassing studies, reviews, and other evidence conducted on human subjects that were published in English from MEDLINE (PubMed), EMBASE, the Cochrane Collaboration, the Agency for Healthcare Research and Quality, and other relevant databases. Additional relevant clinical trials and research studies, published through September 2021, were also considered. This guideline was harmonized with other American Heart Association/American College of Cardiology guidelines published through December 2021.

STRUCTURE: Heart failure remains a leading cause of morbidity and mortality globally. The 2022 heart failure guideline provides recommendations based on contemporary evidence for the treatment of these patients. The recommendations present an evidence-based approach to managing patients with heart failure, with the intent to improve quality of care and align with patients' interests. Many recommendations from the earlier heart failure guidelines have been updated with new evidence, and new recommendations have been created when supported by published data. Value statements are provided for certain treatments with high-quality published economic analyses.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †ACC/AHA Representative. ‡ACC/AHA Joint Committee on Clinical Practice Guidelines Liaison. §ACC/AHA Task Force on Performance Measures Representative. ‖HFSA Representative.

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The American Heart Association requests that this document be cited as follows: Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 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. *Circulation.* 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063

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7.2. Diuretics and Decongestion Strategies in Patients With HF

Recommendations for Diuretics and Decongestion Strategies in Patients With HF Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendations**
1	B-NR	1. In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF.[1–5]
1	B-NR	2. For patients with HF and congestive symptoms, addition of a thiazide (eg, 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.[6]

Synopsis

Bumetanide, furosemide, and torsemide inhibit reabsorption of sodium or chloride at the loop of Henle, whereas thiazide and thiazide-like diuretics act in the distal convoluting tubule and potassium-sparing diuretics (eg, spironolactone) in the collecting duct.[7,8] Loop diuretics are the preferred diuretic agents for use in most patients with HF. Thiazide diuretics such as chlorthalidone or hydrochlorothiazide may be considered in patients with hypertension and HF and mild fluid retention. Metolazone or chlorothiazide may be added to loop diuretics in patients with refractory edema unresponsive to loop diuretics alone. Diuretics should be prescribed to patients who have evidence of congestion or fluid retention. In any patient with a history of congestion, maintenance diuretics should be considered to avoid recurrent symptoms. The treatment goal of diuretic use is to eliminate clinical evidence of fluid retention, using the lowest dose possible to maintain euvolemia. With the exception of MRAs, the effects of diuretics on morbidity and mortality are uncertain.[1–5] As such, diuretics should not be used in isolation but always combined with other GDMT for HF that reduces hospitalizations and prolongs survival. Table 12 lists oral diuretics recommended for use in the treatment of chronic HF. Hyponatremia complicates HF management. If reversing potential causes and free water restriction do not improve hyponatremia, vasopressin antagonists may be helpful in the acute management of

Table 12. Commonly Used Oral Diuretics in Treatment of Congestion for Chronic HF

Drug	Initial Daily Dose	Maximum Total Daily Dose	Duration of Action
Loop diuretics			
Bumetanide	0.5–1.0 mg once or twice	10 mg	4–6 h
Furosemide	20–40 mg once or twice	600 mg	6–8 h
Torsemide	10–20 mg once	200 mg	12–16 h
Thiazide diuretics			
Chlorthiazide	250–500 mg once or twice	1000 mg	6–12 h
Chlorthalidone	12.5–25 mg once	100 mg	24–72 h
Hydrochlorothiazide	25 mg once or twice	200 mg	6–12 h
Indapamide	2.5 mg once	5 mg	36 h
Metolazone	2.5 mg once	20 mg	12–24 h

HF indicates heart failure.

volume overload to decrease congestion while maintaining serum sodium.

Recommendation-Specific Supportive Text

1. Controlled trials with diuretics showed their effects to increase urinary sodium excretion, decrease physical signs of fluid retention, and improve symptoms, QOL, and exercise tolerance.[1–5] Recent data from the nonrandomized OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry revealed reduced 30-day all-cause mortality and hospitalization for HF with diuretic use compared with no diuretic use after hospital discharge for HF.[9] The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond more favorably to other agents in this category (eg, bumetanide, torsemide), potentially because of their increased oral bioavailability.[10–12] In outpatients with HF, diuretic therapy is commonly initiated with low doses, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0 kg daily. Patients may become unresponsive to high doses of diuretic drugs if they consume large amounts of dietary sodium, are taking agents that can block the effects of diuretics (eg, NSAIDs), or have significant impairment of renal function or perfusion.
2. Diuretic resistance can be overcome in several ways, including escalation of loop diuretic dose, intravenous administration of diuretics (bolus or continuous infusion),[6] or combination of different diuretic classes.[13–16] The use of a thiazide or thiazide-like diuretic (eg, metolazone) in combination with a loop diuretic inhibits compensatory distal tubular sodium reabsorption, leading to enhanced natriuresis. However, in a propensity-score matched analysis in patients with hospitalized HF, the addition of metolazone to loop diuretics was found to increase the risk for hypokalemia, hyponatremia, worsening renal function, and mortality, whereas use of higher doses of loop diuretics was not found to adversely affect survival.[17] Although randomized data comparing the 2 diuretic strategies are limited, the DOSE (Diuretic Optimization Strategies Evaluation) trial lends support for the use of high-dose intravenous loop diuretics.[18]

7.3. Pharmacological Treatment* for HFrEF

7.3.1. Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi

Recommendations for Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.[1–5]
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible.[6–13]
1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi 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.[14–18]
Value Statement: High Value (A)		4. In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value.[19–25]
1	B-R	5. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality.[1–5]
Value Statement: High Value (A)		6. In patients with chronic symptomatic HFrEF, treatment with an ARNi instead of an ACEi provides high economic value.[26–29]
3: Harm	B-R	7. ARNi should not be administered concomitantly with ACEi or within 36 hours of the last dose of an ACEi.[30,31]
3: Harm	C-LD	8. ARNi should not be administered to patients with any history of angioedema.[32–35]
3: Harm	C-LD	9. ACEi should not be administered to patients with any history of angioedema.[36–39]

*See Section 7.2, "Diuretics and Decongestion Strategies in Patients with HF," for diuretic recommendations.

Synopsis

Inhibition of the renin-angiotensin system is recommended to reduce morbidity and mortality for patients with HFrEF, and ARNi, ACEi, or ARB are recommended as first-line therapy.[1–18] If patients have chronic symptomatic

HFrEF with NYHA class II or III symptoms and they tolerate an ACEi or ARB, they should be switched to an ARNi because of improvement in morbidity and mortality.[1–5] An ARNi is recommended as de novo treatment in hospitalized patients with acute HF before discharge given improvement in health status, reduction in the prognostic biomarker NT-proBNP, and improvement of LV remodeling parameters compared with ACEi/ARB. Although data are limited, the use of an ARNi may be efficacious as de novo treatment in patients with symptomatic chronic HFrEF to simplify management. ARB may be used as an alternative to ACEi in the setting of intolerable cough, or as alternatives to ACEi and ARNi in patients with a history of angioedema. If patients are switched from an ACEi to an ARNi or vice versa, there should be at least 36 hours between ACEi and ARNi doses.

Recommendation-Specific Supportive Text

1. An ARNi is composed of an ARB and an inhibitor of neprilysin, an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides. In PARADIGM-HF (Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure), an RCT that compared the first approved ARNi, sacubitril-valsartan, with enalapril in symptomatic patients with HFrEF tolerating an adequate dose of either ACEi or ARB, sacubitril-valsartan significantly reduced the composite endpoint of cardiovascular death or HF hospitalization by 20% relative to enalapril.[1] The benefit was observed to a similar extent for death and HF hospitalization and was consistent across prespecified subgroups.[1] Use of an ARNi is more frequently associated with symptomatic hypotension and a comparable incidence of angioedema when compared with enalapril.[1] Sacubitril-valsartan has been approved for patients with symptomatic HF. HF effects and potential off-target effects may be complex with inhibition of the neprilysin enzyme, which has multiple biological targets. Trial data have included ACEi/ARB-naïve patients before ARNi initiation (53% in the PIONEER-HF [Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode] trial and 24% in the TRANSITION [Comparison of Pre- and Post-discharge Initiation of Sacubitril/Valsartan Therapy in HFrEF Patients After an Acute Decompensation Event] trial) and have shown similar efficacy and safety in treatment-naïve patients.[2,3] The PIONEER-HF trial showed that ARNi reduced NT-proBNP levels in patients hospitalized for acute decompensated HF without increased rates of adverse events (worsening renal function, hyperkalemia, symptomatic hypotension, angioedema) when compared with enalapril.[3] Additional outcome analyses suggested reduction in all-cause mortality and rehospitalization for HF but were only hypothesis-generating as exploratory study endpoints. In the open-label TRANSITION trial, patients with HFrEF hospitalized with worsening HF were randomized to start ARNi either before or after discharge.[2] Safety outcomes were similar for both arms, suggesting that early initiation may simplify management (rather than initiating and uptitrating ACEi first and then switching to ARNi).[2] ARNi should be initiated de novo in patients hospitalized with acute HFrEF before discharge in the absence of contraindications. ARNi may be initiated de novo in patients with chronic symptomatic HFrEF to simplify management, although data are limited. The PARADISE-MI (Prospective ARNi vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI) trial[40] will provide information on whether sacubitril-valsartan will significantly reduce the rate of cardiovascular death, HF hospitalization or outpatient HF requiring treatment in patients after acute MI, with LVEF ≤40% and/or pulmonary congestion, and 1 of 8 additional risk-enhancing factors like AF, previous MI, diabetes, compared with the ACEi ramipril; and whether the safety and tolerability of sacubitril-valsartan was comparable to that of ramipril. Thus, at the present time, the efficacy of ARNi in patients with LV dysfunction, and HF in the early post-MI period, remains uncertain.
2. ACEi reduce morbidity and mortality in HFrEF. RCTs clearly establish the benefits of ACE inhibition in patients with mild, moderate, or severe symptoms of HF and in patients with or without CAD.[6–11] Data suggest that there are no differences among available ACEi in their effects on symptoms or survival.[12] ACEi should be started at low doses and titrated upward to doses shown to reduce the risk of cardiovascular events in clinical trials. ACEi can produce angioedema and should be given with caution to patients with low systemic blood pressures, renal insufficiency, or elevated serum potassium (>5.0 mEq/L). If maximal doses are not tolerated, intermediate doses should be tried; abrupt withdrawal of ACE inhibition can lead to clinical deterioration and should be avoided. Although the use of an ARNi in lieu of an ACEi for HFrEF has been found to be superior, for those patients for whom ARNi is inappropriate, continued use of an ACEi for all classes of HFrEF remains strongly advised.
3. ARB have been shown to reduce mortality and HF hospitalizations in patients with HFrEF in large RCTs.[14–16] Long-term treatment with ARB in patients with HFrEF produces hemodynamic,

neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system.[17,18] Unlike ACEi, ARB do not inhibit kininase and are associated with a much lower incidence of cough and angioedema, although kininase inhibition by ACEi may produce beneficial vasodilatory effects. Patients who are intolerant to ACEi because of cough or angioedema should be started on an ARB. ARB should be started at low doses and titrated upward, with an attempt to use doses shown to reduce the risk of cardiovascular events in clinical trials. ARB should be given with caution to patients with low systemic blood pressure, renal insufficiency, or elevated serum potassium (>5.0 mEq/L). Although ARB are alternatives for patients with ACEi-induced angioedema, caution is advised because some patients have also developed angioedema with ARB. For those patients for whom an ACEi or ARNi is inappropriate, use of an ARB remains advised.

4. Several cost-effectiveness analyses consistently found that ACEi therapy provides high value for patients with chronic HF. A model-based analysis, using generic ACEi costs, found ACEi therapy was high value.[19] Previous analyses also found ACEi therapy was high value despite previously higher ACEi costs.[19,21,22,24,25] This includes a trial-based analysis of SOLVD (Studies of Left Ventricular Dysfunction) that modeled long-term outcomes.[21] Previous analyses included a range of clinical scenarios including asymptomatic LV dysfunction[24] and LV dysfunction after MI,[25] with ACEi therapy providing high value in each. There are limited data on the cost-effectiveness of ARBs from 2 clinical trials—a within-trial analysis of Val-HeFT (Valsartan Heart Failure Trial)[23] and an analysis of the ELITE (Evaluation of Losartan in the Elderly) study[20]—which both suggested ARB therapy is high value. The high value of ARB therapy is also supported by its similar efficacy as ACEi therapy and the low-cost generic availability for both medication classes.
5. Patients with chronic stable HFrEF who tolerate ACEi and ARB should be switched to ARNi. In patients with mild-to-moderate HF who were able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently an ARNi (sacubitril-valsartan; 200 mg twice daily, with the ARB component equivalent to valsartan 160 mg), hospitalizations and mortality were significantly decreased with the valsartan-sacubitril compound compared with enalapril.[1] Another RCT and meta-analysis showed improvement in LV remodeling parameters with ARNi compared with enalapril.[4,5]
6. Multiple model-based analyses evaluated the economic value of ARNi therapy compared with ACEi therapy using the results of PARADIGM-HF.[26–29,41] Three high-quality analyses[26,28,29] consistently found costs per QALY <$60 000, which provides high value according to the benchmarks adopted for the current clinical practice guideline. These results were robust to the range of sacubitril-valsartan costs currently seen in care. These results were sensitive to the estimated mortality reduction and duration of treatment effectiveness. ARNi would need to maintain effectiveness beyond the PARADIGM-HF study period (mean, 27 months) to be considered high value.[29] If clinical benefit were limited to 27 months, ARNi would be intermediate value. One additional analysis, based on the PIONEER-HF trial, found that inpatient initiation of ARNi was also high value compared with delayed initiation postdischarge.[27]
7. Oral neprilysin inhibitors, used in combination with ACEi, can lead to angioedema, and concomitant use is contraindicated and should be avoided. A medication that represented a neprilysin inhibitor and an ACEi—omapatrilat—was studied in hypertension and HF, but its development was terminated because of an unacceptable incidence of angioedema.[30,31] and associated significant morbidity. This adverse effect was thought to occur because ACEi and neprilysin break down bradykinin, which can directly or indirectly cause angioedema[31,32] An ARNi should not be administered within 36 hours of switching from or to an ACEi.
8. Omapatrilat, a neprilysin inhibitor (as well as an ACEi and aminopeptidase P inhibitor), was associated with a higher frequency of angioedema than that seen with enalapril in an RCT of patients with HFrEF.[30] In a very large RCT of hypertensive patients, omapatrilat was associated with a 3-fold increased risk of angioedema compared with enalapril.[31] Black patients and patients who smoked were particularly at risk. The high incidence of angioedema ultimately led to cessation of the clinical development of omapatrilat.[33,34] Because of these observations, angioedema was an exclusion criterion in the first large trial assessing ARNi therapy in patients with hypertension[35] and then in the large trial that showed clinical benefit of ARNi therapy in HFrEF.[1] The rates of angioedema were numerically higher in patients treated with ARNi than in patients treated with ACEi in PARADIGM-HF, although this difference did not reach significance.[1] ARNi therapy should not be administered in patients with a history of angioedema because of the concern that it will increase the risk of a recurrence of angioedema.
9. Angioedema attributable to ACEi is thought to result from defective degradation of the vasoactive peptides bradykinin, des-Arg9-BK (a metabolite

of bradykinin), and substance P.[36,37] ACEi should not be administered to patients with any history of angioedema, but ARB do not interfere as directly with bradykinin metabolism and have been associated with low rates of angioedema.[38,39]

7.3.2. Beta Blockers

Recommendation for Beta Blockers Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendation**
1	**A**	1. In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations.[1–3]
Value Statement: High Value (A)		2. In patients with HFrEF, with current or previous symptoms, beta-blocker therapy provides high economic value.[4–8]

Synopsis

Treatment with beta blockers reduces the risk of death and the combined risk of death or hospitalization in patients with HFrEF.[1–3] In addition, this treatment can improve LVEF, lessen the symptoms of HF, and improve clinical status.[1–3,9–11] Clinical trials have shown that beta blockers should be prescribed to all patients when HFrEF is diagnosed, including in-hospital, unless contraindicated or not tolerated.[1–3,9–11] These benefits of beta blockers were observed in patients with or without CAD, and in patients with or without diabetes, older patients, as well as in women and across racial and ethnic groups but not in patients with AF.[1–3,10–12] Even if symptoms do not improve, long-term treatment should be maintained to reduce the risk of major cardiovascular events. Beta blockers should be initiated at low doses, and every effort should be made to achieve the target doses of the beta blockers shown to be effective in major clinical trials, as tolerated[1–3,9,10] (see Section 7.3.8, "GDMT Dosing, Sequencing and Uptitration").

Recommendation-Specific Supportive Text

1. Three beta blockers have been shown to be effective in reducing the risk of death in patients with HFrEF: bisoprolol, sustained-release metoprolol (succinate), and carvedilol.[1–3] The favorable findings with these 3 agents, however, should not be considered a beta-blocker class effect in HFrEF. Other beta blockers are not included in this recommendation for use.[13–15] Even when asymptomatic, or when symptoms are mild or improve with other therapies, beta-blocker therapy is important and should not be delayed until symptoms return or disease progression is documented.[16] Data show that beta blockers can be safely initiated before hospital discharge, provided patients are clinically stabilized and do not require intravenous inotropic therapy for HF.[17] If a contraindication or intolerance are noted, they should be documented, and the patient restarted on beta-blocker therapy in the future, so long as an absolute contraindication is not present. Even if symptoms or LVEF improve, long-term treatment with beta blockers and use of target doses should be maintained to reduce the risk of progression in LV dysfunction or major cardiovascular events.[18,19] Abrupt withdrawal of beta-blocker therapy can lead to clinical deterioration and should be avoided unless indicated.[18]
2. Multiple analyses have shown the high value of beta-blocker therapy among HF patients. A model-based analysis, using generic beta-blocker costs, found beta-blocker therapy was high value.[4] These results were consistent with earlier model-based cost-effectiveness analyses[5–7] and a trial-based economic analysis of the US Carvedilol Heart Failure (CHF) Trials Program.[8] Each of these studies also found treatment with a beta blocker was high value despite using previously higher beta-blocker costs.

7.3.3. Mineralocorticoid Receptor Antagonists (MRAs)

Recommendations for Mineralocorticoid Receptor Antagonists (MRAs) Referenced studies that support the recommendations are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendations**
1	**A**	1. In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 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.[1–3]
Value Statement: High Value (A)		2. In patients with HFrEF and NYHA class II to IV symptoms, MRA therapy provides high economic value.[4–7]
3: Harm	**B-NR**	3. In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia.[8,9]

Synopsis

MRA (also known as aldosterone antagonists or anti-mineralocorticoids) show consistent improvements in all-cause mortality, HF hospitalizations, and SCD across a wide range of patients with HFrEF.[1–3] Patients at risk for renal dysfunction or hyperkalemia require close monitoring, and eGFR ≤30 mL/min/1.73 m^2 or serum potassium ≥5.0 mEq/L are contraindications to MRA initiation.[10,11] Because of the higher selectivity of eplerenone for the aldosterone receptor, adverse effects such as gynecomastia and vaginal bleeding

are observed less often in patients who take eplerenone than in those who take spironolactone.

Recommendation-Specific Supportive Text

1. Clinical trials taken on MRA together—RALES (Randomized Aldactone Evaluation Study)[1] randomized highly symptomatic patients with LVEF ≤35%; EPHESUS (Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study)[2] randomized patients post-MI with LVEF ≤40%; and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure)[3] randomized patients with mild symptoms and LVEF ≤30%—suggest a benefit of MRA across the spectrum of HFrEF, inclusive of a wide range of etiologies and disease severities. Initiation in the ambulatory or hospital setting is appropriate.[12] The starting dose of spironolactone and eplerenone is 25 mg orally daily, increased to 50 mg daily orally after a month; for eGFR 31 to 49 mL/min/1.73 m^2, dosing should be reduced by half. Regular checks of serum potassium levels and renal function should be performed according to clinical status, approximately 1 week, then 4 weeks, then every 6 months after initiating or intensifying MRA, with more frequent testing for clinical instability. We elected to remove the 2013 recommendation "Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated" because the new recommendation covers the spectrum of symptomatic patients with HF.
2. The economic value of MRA therapy was assessed by both RCTs (RALES[5] and EPHESUS[6,7]) and a model-based analysis.[4] The model-based analysis used generic MRA costs and found therapy was high value with a cost per QALY of under $1000.[4] The earlier trial-based economic analyses of MRAs from RALES and EPHESUS also found MRA therapy was high value despite using previously higher MRA costs.[5–7]
3. Spironolactone and eplerenone are partially excreted through the kidneys, raising concerns about safety when eGFR is ≤30 mL/min/1.73 m^2.[10,11] Spironolactone and eplerenone decrease renal potassium excretion, raising the risk of hyperkalemia, particularly when MRA is initiated at serum potassium ≥5.0 mEq/L and continued ≥5.5 mEq/L. The incidence of clinically significant hyperkalemia events was <1% in EPHESUS and EMPHASIS-HF, without a significant difference between eplerenone and placebo.[2,3] however, in the closely monitored setting of a RCT with enrollment of younger patients with fewer multiple chronic conditions than seen in the general HFrEF population, safety may be overstated. Observational data have raised concerns about less favorable outcomes of MRA use for HFrEF during usual care.[8,9] Coadministration of MRA with ACEi or ARB mildly increases the risk of hyperkalemia. Hyperkalemia risk was lower with ARNi in patients with chronic HF in the PARADIGM-HF trial[13] but not different in patients with HF who were decompensated in the PIONEER-HF trial[14] when compared with ACEi. Diarrhea causing dehydration or loop diuretic therapy interruption, because of worsening renal function or hyperkalemia, should be a consideration for temporarily holding the MRA. The development of worsening renal function or hyperkalemia is often a reflection of acute clinical change or progressive disease, prompting careful evaluation of the entire medical regimen and other causes of hyperkalemia, in addition to holding the MRA. The efficacy of the use of potassium binders (eg, patiromer, sodium zirconium cyclosilicate) to improve outcomes by facilitating continuation of MRA is uncertain[15,16] and is addressed in Section 7.3.6, "Other Drug Treatment."

7.3.4. Sodium-Glucose Cotransporter 2 Inhibitors

Recommendation for SGLT2i Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendation**
1	**A**	1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.[1,2]
Value Statement: Intermediate Value (A)		2. In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value.[3,4]

Synopsis

Several RCTs in patients with type 2 diabetes and either established CVD or high risk for CVD have shown that SGLT2i prevent HF hospitalizations compared with placebo.[5–7] The overall 31% reduction in HF hospitalizations was noted irrespective of the presence or absence of preexisting HF, although only 10% to 14% of participants had HF at baseline. The benefit appears independent of the glucose-lowering effects.[8] Therefore, several trials were launched to examine the efficacy of SGLT2i on outcomes in patients with HF, irrespective of the presence of type 2 diabetes. The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial and EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) showed the benefit of SGLT2i (dapagliflozin and empagliflozin, respectively) versus placebo on outcomes (median follow-up, 16–18

months).[1,2] Patients enrolled had symptomatic chronic HFrEF (LVEF ≤40%, NYHA class II to IV, and elevated natriuretic peptides) and were already on GDMT. Important exclusions were eGFR <20 (EMPEROR-Reduced) or <30 mL/min/1.73 m^2 (DAPA-HF), type 1 diabetes, or lower SBP <95 to 100 mm Hg.

Recommendation-Specific Supportive Text

1. In the DAPA-HF and EMPEROR-Reduced trials, SGLT2i compared with placebo reduced the composite of cardiovascular death or HF hospitalization by approximately 25%.[1,2,9] The benefit in reduction of HF hospitalization was greater (30%) in both trials.[9] Risk of cardiovascular death was significantly lowered (18%) with dapagliflozin, as was risk of all-cause mortality (17%). Although no significant cardiovascular mortality benefit was observed with empagliflozin in a meta-analysis of DAPA-HF and EMPEROR-Reduced trials, SGLT2i therapy was associated with a reduction in all-cause mortality and cardiovascular death.[9] The benefits in both trials were seen irrespective of baseline diabetes status. Furthermore, serious renal outcomes were less frequent, and the rate of decline in eGFR was slower in patients treated with SGLT2i.[1,2,9] In the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes And Worsening Heart Failure) trial, patients with diabetes and HF hospitalization (79%: LVEF, <50%) were enrolled before discharge or within 3 days of discharge. Sotagliflozin, a dual inhibitor of sodium-glucose co-transporters 1 and 2, reduced the combined endpoint of cardiovascular death, HF hospitalization, or urgent HF visits by 33%[10] but has not been approved by the US Food and Drug Administration (FDA) as of 2021. Although SGLT2i increased risk for genital infections, they were otherwise well tolerated in the trials. As the use of SGLT2i is translated into clinical practice, caution is warranted for euglycemic ketoacidosis, genital and soft tissue infections, and adjustment of diuretics, if needed, to prevent volume depletion.[11]
2. Two model-based analyses evaluated the economic value of dapagliflozin therapy compared with usual care based on the results of the DAPA-HF trial.[3,4] Both analyses found costs per QALY between $60 000 and $90 000, which is consistent with intermediate value according to the benchmarks adopted for the current guideline. The results were most sensitive to the magnitude of cardiovascular mortality reduction, with a ≥8% reduction in cardiovascular mortality necessary for a cost per QALY below $150 000 in 1 study.[3] There are a wide range of costs currently seen with dapagliflozin. These 2 analyses estimated a cost per QALY below $50 000 with annual dapagliflozin costs of $3240 (43% reduction from main analysis) and $2500 (40% reduction from main analysis), respectively.[3,4] A smaller reduction in drug cost would lead to a cost per QALY of under $60 000, the threshold for high value in this guideline.

7.3.5. Hydralazine and Isosorbide Dinitrate

Recommendations for Hydralazine and Isosorbide Dinitrate
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	1. 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.[1,2]
Value Statement: High Value (B-NR)		2. For patients self-identified as African American with NYHA class III to IV HFrEF who are receiving optimal medical therapy with ACEi or ARB, beta blockers, and MRA, the combination of hydralazine and isosorbide dinitrate provides high economic value.[3]
2b	C-LD	3. 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.[4,5]

Synopsis

Two RCTs, V-HeFT I (Vasodilator Heart Failure Trial) and A-HeFT (African-American Heart Failure Trial), established benefit of the combination of hydralazine-isosorbide dinitrate in self-identified African Americans.[2,4] A-HeFT was terminated early because of evidence of remarkable benefit, but the result is vulnerable to a small number of events and the exigencies of early cessation of RCTs.[2] The benefit in both trials was seen only at doses achieved in those trials that are higher than doses typically used in clinical practice and with short-acting nitrate therapy.[2,4] Uptake of this regimen has been modest as a result of the complexity of the medical regimen and the array of drug-related adverse effects.[5] Even when prescribed, there is marked underusage based on very low prescription refill rates. Race-based medical therapy remains a challenging issue, as well, with ongoing research now focused on biological hypotheses, particularly absence of European ancestry, which may be associated with responsiveness to this combination. There are insufficient data to guide the use of hydralazine-isosorbide dinitrate with ARNi. In patients with HFrEF who cannot receive first-line agents such as ARNi, ACEi, or ARB, referral to a HF specialist can provide guidance for further management because the use of hydralazine and isosorbide dinitrate in these patients is uncertain.

Recommendation-Specific Supportive Text

1. In a large-scale trial that compared the vasodilator combination with placebo, the use of hydralazine and isosorbide dinitrate reduced mortality in patients with HF treated with digoxin and diuretics but not an ACEi or beta blocker.[4] However, in 2 other trials that compared the vasodilator combination with an ACEi, the ACEi produced more favorable effects on survival.[6,7] A post hoc retrospective analysis of these vasodilator trials showed particular efficacy of isosorbide dinitrate and hydralazine in the African American cohort.[1] In a subsequent trial, which was limited to patients self-identified as African American, the addition of a fixed-dose combination of hydralazine and isosorbide dinitrate to standard therapy with an ACEi or ARB, a beta blocker, and MRA offered significant benefit.[2] Thus, the combination of hydralazine and isosorbide dinitrate is appropriate for African Americans with HFrEF who remain symptomatic despite concomitant use of ACEi (or ARB), beta blockers, and MRA. There are insufficient data for concomitant use with ARNi.
2. The economic value of hydralazine and isosorbide nitrate therapy was assessed by the A-HeFT trial.[3] This analysis found hydralazine and isosorbide dinitrate increased survival and reduced health care costs over the 12.8-month trial. Extrapolating beyond the trial, the analysis found hydralazine and isosorbide dinitrate remained high value over a lifetime with a cost per life-year <$60 000 despite conservative assumptions regarding the durability of therapy effectiveness and previously higher hydralazine and isosorbide dinitrate costs.
3. It is unclear if a benefit of hydralazine-isosorbide dinitrate (suggested in a trial before the use of ACEi)[4] exists for non–African Americans with HFrEF. Despite the lack of data with the vasodilator combination in patients who are intolerant of ACEi or ARB, especially those with renal insufficiency, the combined use of hydralazine and isosorbide dinitrate might be considered as a therapeutic option in such patients. Although the potential benefit is unknown and has not been shown in recent observational datasets,[5] in V-HeFT I, the use of hydralazine and isosorbide dinitrate reduced mortality in patients with HF treated with digoxin and diuretics, compared with placebo.[4] If patients are unable to tolerate first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance, hypotension, or renal insufficiency, referral to a HF specialist can provide guidance for further management, and the use of hydralazine and isosorbide dinitrate in these patients might be considered.

7.3.6. Other Drug Treatment

Recommendations for Other Drug Treatment
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
2b	B-R	1. 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.[1–4]
2b	B-R	2. In patients with HF who experience hyperkalemia (serum potassium level ≥5.5 mEq/L) while taking a renin-angiotensin-aldosterone system inhibitor (RAASi), the effectiveness of potassium binders (patiromer, sodium zirconium cyclosilicate) to improve outcomes by facilitating continuation of RAASi therapy is uncertain.[5,6]
3: No Benefit	B-R	3. In patients with chronic HFrEF without a specific indication (eg, venous thromboembolism [VTE], AF, a previous thromboembolic event, or a cardioembolic source), anticoagulation is not recommended.[7–9]

Synopsis

Trials in prevention of CVD, including HF, showed that omega-3 PUFA supplementation results in a 10% to 20% risk reduction in fatal and nonfatal cardiovascular events when used with other evidence-based therapies.[2,3,10] Hyperkalemia is common in HF and can lead to arrhythmias and underuse of GDMT.[11,12] Two newer gastrointestinal potassium-binding agents—patiromer and sodium zirconium cyclosilicate—have been shown to lower potassium levels and enable treatment with a RAASi in patients with HF.[5,6,13]

Recommendation-Specific Supportive Text

1. Supplementation with omega-3 PUFA has been evaluated as an adjunctive therapy for CVD and HF.[14] The GISSI-HF (Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure) trial showed a reduction in death among post-MI patients taking 1 g of omega-3 PUFA (850–882 mg of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] as ethyl esters in the ratio of 1:1.2).[10] A post hoc subgroup analysis revealed that this reduction in mortality and SCD was concentrated in the approximately 2000 patients with reduced LVEF.[10] The GISSI-HF investigators randomized symptomatic patients with HF to 1 g daily of omega-3 PUFA (850–882 mg of EPA-DHA) or placebo. Death from any cause was reduced from 29% with placebo to 27% in those treated with omega-3 PUFA.[2] The outcome of death or admission to hospital for a cardiovascular event was also significantly reduced. The REDUCE-IT trial randomized patients with established CVD

or diabetes with risk factors to 2 g of icosapent ethyl (a highly purified EPA) twice daily or placebo and showed a reduced risk for the composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina.[3] In reported studies, omega-3 PUFA therapy has been well tolerated. Recent studies have reported that in patients with cardiovascular risk treated with omega-3 fatty acid, there may be a dose-related risk of AF.[3,15,16]

2. Hyperkalemia is common in HF as a result of the syndrome itself, comorbidities (diabetes, CKD), and use of RAASi, and can increase the risk for ventricular arrhythmias and mortality.[11] Hyperkalemia results in dose reductions or discontinuation of RAASi, compromising their cardiorenal benefit in HF.[12] Two newer gastrointestinal potassium binders—patiromer (RLY5016) and sodium zirconium cyclosilicate (SZC)—remove potassium by exchanging cations (calcium for patiromer, and sodium and hydrogen for SZC), leading to increased fecal excretion. Both agents have been FDA approved for treatment of hyperkalemia for patients receiving RAASi. In the PEARL-HF (Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder in patients with chronic heart failure) trial, patiromer led to lower potassium levels, less hyperkalemia, and a higher proportion of patients able to increase spironolactone dose to 50 mg daily compared with placebo.[5] The HARMONIZE (Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance) trial included 94 patients (out of 258 total) with HF (87 of whom entered the double-blind phase).[6,13] The SZC groups achieved lower potassium levels overall compared with placebo, and a higher proportion maintained normokalemia (potassium levels, <5.1 mEq/L). Whether patiromer or SZC improve clinical outcomes is under investigation. Adverse effects for the newer potassium binders include hypomagnesemia (for patiromer) and edema (for SZC).
3. In several retrospective analyses, the risk of thromboembolic events was not lower in patients with HF taking warfarin than in patients not treated with antithrombotic drugs.[17–19] The use of warfarin was associated with a reduction in major cardiovascular events and death in patients with HF in some studies but not in others.[20–22] An RCT that compared the outcome of patients with HFrEF assigned to aspirin, warfarin, or clopidogrel found that no therapy was superior.[7] Another trial that compared aspirin with warfarin in patients with reduced LVEF, sinus rhythm, and no cardioembolic source showed no difference in either the primary outcome of death, stroke, or intracerebral hemorrhage, and no difference in the combined outcome of death, ischemic stroke, intracerebral hemorrhage, MI, or HF hospitalization.[8] There was a significant increase in major bleeding with warfarin. A trial of rivaroxaban in patients with HFrEF, CAD, and normal sinus rhythm showed no difference in mortality, MI, and stroke compared with placebo.[9] Therefore, there is no evidence of benefit for anticoagulation in HF patients without a specific indication (eg, VTE, AF, a previous thromboembolic event, or a cardioembolic source).

7.3.7. Drugs of Unproven Value or That May Worsen HF

Recommendations for Drugs of Unproven Value or Drugs That May Worsen HF
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
3: No Benefit	A	1. In patients with HFrEF, dihydropyridine calcium channel-blocking drugs are not recommended treatment for HF.[1,2]
3: No Benefit	B-R	2. In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies.[3–9]
3: Harm	A	3. In patients with HFrEF, nondihydropyridine calcium channel-blocking drugs are not recommended.[10–13]
3: Harm	A	4. In patients with HFrEF, class IC antiarrhythmic medications and dronedarone may increase the risk of mortality.[14–16]
3: Harm	A	5. In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations.[17–21]
3: Harm	B-R	6. In patients with type 2 diabetes and high cardiovascular risk, the dipeptidyl peptidase-4 (DPP-4) inhibitors saxagliptin and alogliptin increase the risk of HF hospitalization and should be avoided in patients with HF.[22–24]
3: Harm	B-NR	7. In patients with HFrEF, NSAIDs worsen HF symptoms and should be avoided or withdrawn whenever possible.[25–28]

Synopsis

Although there is strong evidence for benefit with selected medications for HFrEF as outlined in Section 7.3, "Pharmacological Treatment for HF With Reduced Ejection Fraction (HFrEF)," there remain several classes of medications that have either unproven value or potential for harm (Table 13). These recommendations are not exhaustive but focus on the most relevant and commonly encountered medications in the management of patients with HFrEF: calcium channel blockers; antiarrhythmic agents; NSAIDs; medications for treatment of type 2 diabetes including thiazolidinediones and DPP-4 inhibitors; and vitamins, hormones, and nutritional supplements.

Table 13. Selected Prescription Medications That May Cause or Exacerbate HF

Drug or Therapeutic Class	Associated With HF		Magnitude of HF Induction or Precipitation	LOE for HF Induction or Precipitation	Possible Mechanism(s)	Onset
	Causes Direct Myocardial Toxicity	Exacerbates Underlying Myocardial Dysfunction				
COX, nonselective inhibitors (NSAIDs)		X	Major	B	Prostaglandin inhibition leading to sodium and water retention, increased systemic vascular resistance, and blunted response to diuretics	Immediate
COX, selective inhibitors (COX-2 inhibitors)		X	Major	B		
Thiazolidinediones		X	Major	A	Possible calcium channel blockade	Intermediate
Saxagliptin		X	Major	A	Unknown	Intermediate to delayed
Alogliptin		X	Major	A		
Flecainide		X	Major	A	Negative inotrope, proarrhythmic effects	Immediate to intermediate
Disopyramide		X	Major	B		
Sotalol		X	Major	A	Proarrhythmic properties, beta blockade	Immediate to intermediate
Dronedarone		X	Major	A	Negative inotrope	
Alpha-1 blockers						
Doxazosin		X	Moderate	B	Beta-1-receptor stimulation with increases in renin and aldosterone	Intermediate to delayed
Diltiazem		X	Major	B	Negative inotrope	Immediate to intermediate
Verapamil		X	Major	B		
Nifedipine		X	Moderate	C		

COX indicates cyclo-oxygenase; HF, heart failure; LOE, Level of Evidence; and NSAID, nonsteroidal anti-inflammatory drug.
Adapted from Page RL 2nd et al.[57] Copyright 2016 American Heart Association Inc.

Recommendation-Specific Supportive Text

1. Second-generation dihydropyridine calcium channel blockers, including amlodipine and felodipine, have greater selectivity for calcium channels in vascular smooth muscle cells and less myocardial depressant activity. By reducing peripheral vasoconstriction and LV afterload, calcium channel blockers were thought to have a potential role in the management of chronic HF. The PRAISE-1 (Prospective Randomized Amlodipine Survival Evaluation-1) study showed a reduction in mortality in the subgroup of patients with nonischemic cardiomyopathy who received amlodipine.[1] However, in the PRAISE-2 (Prospective Randomized Amlodipine Survival Evaluation 2) trial, which enrolled only patients with nonischemic cardiomyopathy, no survival benefit was observed, indicating the limitations of conclusions derived from subgroup analyses.[29] However, dihydropyridine calcium channel blockers may be used for treatment of hypertension in patients who have elevated blood pressure despite optimization of GDMT.
2. Many nutritional supplements and hormonal therapies have been proposed for the treatment of HF.[3–9,30,31] Ultimately, most studies are limited by small sample sizes, surrogate endpoints, or nonrandomized design.[32,33] In addition, adverse effects and drug-nutraceutical interactions remain unresolved. There is a lack of evidence of benefit from vitamin D,[3–5] thiamine,[34–36] carnitine,[37] and taurine[38,39] and potential harm from vitamin E.[6,7] The largest RCT of coenzyme Q10—Q-SYMBIO (Coenzyme Q10 as adjunctive treatment of chronic heart failure with focus on SYMptoms, Biomarker status [Brain-Natriuretic Peptide], and long-term Outcome [hospitalisations/mortality])—showed no changes in NYHA functional classification at 16 weeks, although the incidence of major adverse cardiovascular events at 2 years was significantly reduced (hazard ratio, 0.50; 95% CI, 0.32-0.80; P=0.003).[8] Despite these findings, concerns about slow recruitment in this trial have tempered enthusiasm for coenzyme Q10 supplementation in clinical practice.[9,31] Hormonal therapies have been proposed for the treatment of HF, but trials have shown a neutral effect of testosterone,[40,41] growth hormone,[30,42] and thyroid hormone[43–45] in HF outcomes.
3. Nondihydropyridine calcium channel blockers—diltiazem and verapamil—are myocardial depressants and generally not well tolerated in HF. Verapamil had no impact of survival or major cardiac events post-MI, including in those patients with HFrEF after acute MI.[10] In patients with nonischemic

cardiomyopathy, diltiazem had no impact on mortality[13] but, in HFrEF after acute MI, diltiazem was associated with a higher risk of recurrent HF.[11,12]

4. In the CAST (Cardiac Arrhythmia Suppression) trial, patients with asymptomatic ventricular arrhythmias post-MI on the class IC antiarrhythmics encainide or flecainide had increased mortality.[14] The applicability of CAST to patients without recent MI or to other class I antiarrhythmic drugs is uncertain, but class IC antiarrhythmic agents are generally avoided in patients with structural heart disease. In ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease Study), for the class III antiarrhythmic dronedarone, patients with HFrEF who were hospitalized had increased mortality.[16] In the SWORD (Survival With ORal D-sotalol) trial of the class III antiarrhythmic sotalol, patients with HF post-MI had increased mortality.[15] However, SWORD was published in 1996, and whether sotalol would be harmful in the current era of GDMT and ICDs is uncertain; sotalol may be used for refractory atrial-ventricular arrhythmias with close monitoring for decompensation. Amiodarone[46,47] and dofetilide[48,49] are the only antiarrhythmic agents with neutral effects on mortality in clinical trials of patients with HFrEF. Class IA antiarrhythmic agents such as quinidine and class IB agents such as mexiletine have not been studied and may be indicated for the management of refractory ventricular arrhythmias in the context of the individual patient's risk benefit calculus and in conjunction with electrophysiology consultation.
5. Thiazolidinediones increase insulin sensitivity by activating nuclear peroxisome proliferator-activated receptor gamma (PPAR-γ). Expressed in virtually all tissues, PPAR-γ also regulates sodium reabsorption in the collecting ducts of the kidney. In observational cohort studies,[17] meta-analysis,[18] and clinical trials,[19–21] thiazolidinediones have been associated with increased incidence of fluid retention and HF events in those patients with[19,21]or without[18,20]a previous history of HF.
6. DPP-4 is a cell-surface enzyme that deactivates several peptides include glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1. DPP-4 inhibitors affect glucose regulation through multiple mechanisms, including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, and reduction of postprandial glucagon and of food intake. The impact of DPP-4 inhibitors on cardiovascular outcomes in patients with diabetes and high cardiovascular risk has been assessed in multiple RCTs. Saxagliptin increased the risk of hospitalization for HF,[22] as did alogliptin in a post hoc analysis including only patients with no HF history,[23,50] but sitagliptin[51,52]and linagliptin[53–55] did not; these findings may have been a result of baseline differences in the use of metformin, thiazolidinediones, and insulin, which also affect HF risk. The FDA recommends discontinuation specifically of saxagliptin and alogliptin in patients who develop HF,[56] and whether the risk of worsening HF is a class effect of DPP-4 inhibitors is unclear.
7. NSAIDs inhibit the synthesis of renal prostaglandins, which mediate vasodilation in the kidneys and directly inhibit sodium resorption in the thick ascending loop of Henle and collecting tubule. Hence, NSAIDs can cause sodium and water retention and blunt the effects of diuretics. Several observational cohort studies have revealed increased morbidity and mortality in patients with HF using either nonselective or selective NSAIDs.[25–28]

7.3.8. GDMT Dosing: Sequencing and Uptitration

Recommendations for GDMT Dosing: Sequencing and Uptitration Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	A	1. In patients with HFrEF, titration of guideline-directed medication dosing to achieve target doses showed to be efficacious in RCTs is recommended, to reduce cardiovascular mortality and HF hospitalizations, unless not well tolerated.[1–10]
2a	C-EO	2. In patients with HFrEF, titration and optimization of guideline-directed medications as frequently as every 1 to 2 weeks depending on the patient's symptoms, vital signs, and laboratory findings can be useful to optimize management.

Synopsis

Clinical trials of ACEi, ARB, ARNi, beta blockers, and most other HFrEF medications had therapy initiated at low dose by trial protocol.[1–9,11–14] If the initial dose was tolerated, the protocol would then direct the uptitration of medication dose over time to a specified target dose (Table 14), unless not well tolerated. Even if symptoms improved or other indicators of response were shown at lower doses, the medication dose would still be increased to the trial-defined target doses. Because these target doses were the ones that established the efficacy and safety of these medications in HFrEF and serve as the basis of the guideline recommendations (Table 15), use of these target doses is recommended, if tolerated.[1–9,11–14] Use of all 4 drug classes has been estimated to reduce all-cause mortality by 73% compared with no treatment.[15]

If the target dose cannot be achieved or is not well tolerated, then the highest tolerated dose is recommended.

Table 14. Drugs Commonly Used for HFrEF (Stage C HF)

Drug	Initial Daily Dose(s)	Target Doses(s)	Mean Doses Achieved in Clinical Trials	References
ACEi				
Captopril	6.25 mg 3 times daily	50 mg 3 times daily	122.7 mg total daily	19
Enalapril	2.5 mg twice daily	10–20 mg twice daily	16.6 mg total daily	3
Fosinopril	5–10 mg once daily	40 mg once daily	NA	…
Lisinopril	2.5–5 mg once daily	20–40 mg once daily	32.5–35.0 mg total daily	17
Perindopril	2 mg once daily	8–16 mg once daily	NA	…
Quinapril	5 mg twice daily	20 mg twice daily	NA	…
Ramipril	1.25–2.5 mg once daily	10 mg once daily	NA	…
Trandolapril	1 mg once daily	4 mg once daily	NA	…
ARB				
Candesartan	4–8 mg once daily	32 mg once daily	24 mg total daily	20
Losartan	25–50 mg once daily	50–150 mg once daily	129 mg total daily	18
Valsartan	20–40 mg once daily	160 mg twice daily	254 mg total daily	21
ARNi				
Sacubitril-valsartan	49 mg sacubitril and 51 mg valsartan twice daily (therapy may be initiated at 24 mg sacubitril and 26 mg valsartan twice daily)	97 mg sacubitril and 103 mg valsartan twice daily	182 mg sacubitril and 193 mg valsartan total daily	22
Beta blockers				
Bisoprolol	1.25 mg once daily	10 mg once daily	8.6 mg total daily	1
Carvedilol	3.125 mg twice daily	25–50 mg twice daily	37 mg total daily	23
Carvedilol CR	10 mg once daily	80 mg once daily	NA	…
Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg once daily	200 mg once daily	159 mg total daily	11
Mineralocorticoid receptor antagonists				
Spironolactone	12.5–25 mg once daily	25–50 mg once daily	26 mg total daily	6
Eplerenone	25 mg once daily	50 mg once daily	42.6 mg total daily	13
SGLT2i				
Dapagliflozin	10 mg once daily	10 mg once daily	9.8 mg total daily	8
Empagliflozin	10 mg once daily	10 mg once daily	NR	9
Isosorbide dinitrate and hydralazine				
Fixed dose combination	20 mg isosorbide dinitrate and 37.5 mg hydralazine 3 times daily	40 mg isosorbide dinitrate and 75 mg hydralazine 3 times daily	90 mg isosorbide dinitrate and ~175 mg hydralazine total daily	10
Isosorbide dinitrate and hydralazine	20–30 mg isosorbide dinitrate and 25–50 mg hydralazine 3–4 times daily	120 mg isosorbide dinitrate total daily in divided doses and 300 mg hydralazine total daily in divided doses	NA	24
I_f Channel inhibitor				
Ivabradine	5 mg twice daily	7.5 mg twice daily	12.8 total daily	25–27
Soluble guanylate cyclase stimulator				
Vericiguat	2.5 mg once daily	10 mg once daily	9.2 mg total daily	28
Digoxin	0.125–0.25 mg daily (modified according to monogram)	Individualized variable dose to achieve serum digoxin concentration 0.5–<0.9 ng/mL	NA	29,30

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CR, controlled release; CR/XL, controlled release/extended release; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NA, not applicable; NR, not reported; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

There are no direct data showing that use of lower doses of HFrEF medications among patients, where higher target doses could be tolerated, would produce the same or similar degree of clinical benefit. In trials that have evaluated dose response for outcomes, composite event rates were lower with target doses compared with lower dose.[16–18]

Table 15. Benefits of Evidence-Based Therapies for Patients With HFrEF[3–6,8,10–14,23,31–42]

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal RCTs, %	NNT to Prevent All-Cause Mortality Over Time*	NNT for All-Cause Mortality (Standardized to 12 mo)	NNT for All- Cause Mortality (Standardized to 36 mo)
ACEi or ARB	17	22 over 42 mo	77	26
ARNi†	16	36 over 27 mo	80	27
Beta blocker	34	28 over 12 mo	28	9
Mineralocorticoid receptor antagonist	30	9 over 24 mo	18	6
SGLT2i	17	43 over 18 mo	63	22
Hydralazine or nitrate‡	43	25 over 10 mo	21	7
CRT	36	12 over 24 mo	24	8
ICD	23	14 over 60 mo	70	23

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; NNT, number needed to treat; RCT, randomized controlled trial; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

*Median duration follow-up in the respective clinical trial.

†Benefit of ARNi therapy incremental to that achieved with ACEi therapy. For the other medications shown, the benefits are based on comparisons to placebo control.

‡Benefit of hydralazine-nitrate therapy was limited to African American patients in this trial.

Recommendation-Specific Supportive Text

1. The use of these specific medications for HFrEF should involve initiation at low-starting doses, uptitration at specified intervals as tolerated, and achieving-maintaining the target doses shown to be effective in major clinical trials. Every effort should be made by clinicians to achieve and maintain the clinical trial–defined target doses (Table 13) of guideline-directed medications, as long as they are well tolerated by the patient. Patients should be monitored for changes in heart rate, blood pressure, electrolytes, renal function, and symptoms during this uptitration period. Planned uptitration of a HF medication should be delayed until any adverse effects observed with lower doses have resolved. When such a strategy is used for dose titration, most patients (approximately 70%–85%) enrolled in clinical trials who received these medications were able to tolerate short-, intermediate-, and long-term treatment with these agents and achieve and maintain the trial defined target dose.[1–9,11–14] Repeated attempts at uptitration can result in optimization, even if initial attempts may fail. In patients with HFrEF, beta blockers provide dose-dependent improvements in LVEF, reduction in HF hospitalizations, and reduction in all-cause mortality.[17] Trials of lower versus higher dose of ACEi and ARB have shown lower risk of cardiovascular death or HF hospitalization with higher doses, with similar safety and tolerability.[17,18]
2. Initiation and titration should be individualized and optimized without delay according to patient's symptoms, vital signs, functional status, tolerance, renal function, electrolytes, comorbidities, specific cause of HF, and ability of follow-up. In patients with HFrEF, simultaneous initiation or sequencing, and order of guideline-directed medications are usually individualized according to patient's symptoms, vital signs, functional status, tolerance, renal function, electrolytes, comorbidities, specific cause of HF, and ability of follow-up, and does not necessarily need to be done according to the sequence of trial publications and should not be delayed.

7.3.9. Additional Medical Therapies

7.3.9.1. Management of Stage C HF: Ivabradine

Recommendation for the Management of Stage C HF: Ivabradine Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendation**
2a	**B-R**	1. 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.[1,2]

Synopsis

Heart rate is a strong predictor of cardiovascular outcomes in the general population and in patients with CVD, including HF. The SHIFT (Ivabradine and Outcomes in Chronic Heart Failure) trial tested the hypothesis that reducing heart rate in patients with HF improves cardiovascular outcomes.[1] SHIFT demonstrated the efficacy of ivabradine, a sinoatrial node modulator that selectively inhibits the I_f current, in reducing the composite endpoint of cardiovascular death or HF hospitalization in patients with HF. See Figure 7 for a summary of additional medical therapy recommendations.

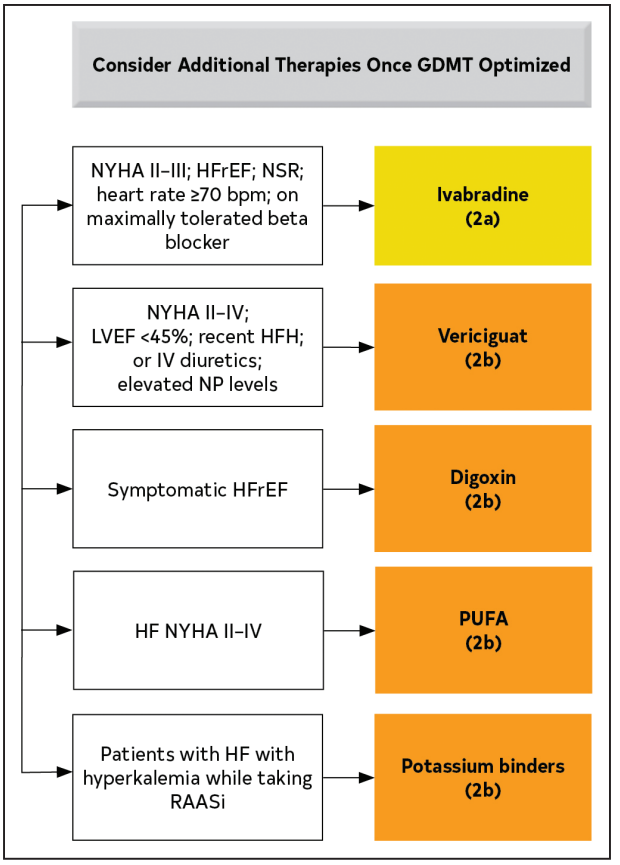

Figure 7. Additional Medical Therapies for Patients With HFrEF. Colors correspond to COR in Table 2. Recommendations for additional medical therapies that may be considered for patients with HF are shown. GDMT indicates guideline-directed medical therapy; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; MV, mitral valve; MR, mitral regurgitation; NP, natriuretic peptide; NSR, normal sinus rhythm; NYHA, New York Heart Association; and RAASi, renin-angiotensin-aldosterone system inhibitors.

Recommendation-Specific Supportive Text

1. Although the primary outcome in SHIFT was a composite of hospitalization and cardiovascular death, the greatest benefit was a reduction in HF hospitalization. SHIFT included patients with HFrEF and LVEF ≤35% who were in sinus rhythm with a resting heart rate of ≥70 bpm. Participants were predominantly NYHA class II and III. Participants had been hospitalized for HF in the preceding 12 months and were on stable GDMT for 4 weeks before initiation of ivabradine therapy.[1–4] The target of ivabradine is heart rate, and the benefit of ivabradine results from a reduction in heart rate. However, only 25% of patients studied in SHIFT were on optimal doses of beta-blocker therapy. Given the well-proven mortality benefits of beta-blocker therapy, these agents should be initiated and uptitrated to target doses, as tolerated, before assessing the resting heart rate for consideration of ivabradine initiation.[5,6]

7.3.9.2. Pharmacological Treatment for Stage C HFrEF: Digoxin

Recommendation for the Pharmacological Treatment for Stage C HFrEF: Digoxin Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendation**
2b	B-R	1. In patients with symptomatic HFrEF despite GDMT (or who are unable to tolerate GDMT), digoxin might be considered to decrease hospitalizations for HF.[1,2]

Synopsis

To date, there has been only 1 large-scale, RCT of digoxin in patients with HF.[1] This trial, which predated current GDMT, primarily enrolled patients with NYHA class II to III HF and showed that treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization. The trial also found no significant effect on health-related QOL in a subset of the trial patients.[3] The effect of digoxin on hospitalizations has been supported by retrospective analyses and meta-analyses.[2,4–6] Additionally, observational studies and retrospective analyses have shown improvement in symptoms and exercise tolerance in mild to moderate HF; however, they have mostly shown either lack of mortality benefit or increased mortality associated with digoxin.[7] The benefit in patients on current GDMT is unclear because most trials preceded current GDMT. Thus, use of digoxin requires caution in patients with HF and is reserved for those who remain symptomatic despite optimization of GDMT.

Recommendation-Specific Supportive Text

1. Digoxin is usually initiated at a low dose because higher doses are rarely required in the management of HF and are potentially detrimental. Two retrospective analyses of large-scale clinical trials have shown a linear relationship between mortality and digoxin serum concentration in patients with AF and at risk for stroke, including those with HF, and in patients with HF. The risk of death was independently associated with serum digoxin concentration, with a significantly higher risk observed in those with concentrations ≥1.2 ng/mL and ≥1.6 ng/mL.[8,9] The benefit of digoxin in patients with HF remains controversial. GDMT is expected to be optimized before considering the addition of digoxin. Clinical worsening after withdrawal of digoxin has been shown.[10] Therapy with digoxin may either be continued in the absence of a contraindication or discontinued with caution.[11] Therapy with digoxin is commonly initiated and maintained at a dose of 0.125 to 0.25 mg daily. Low doses (0.125 mg daily or every other day) should be used initially if the patient is >70 years of

age, has impaired renal function, or has a low lean body mass. Higher doses (eg, digoxin 0.375 to 0.50 mg daily) are rarely used or needed in the management of patients with HF.

7.3.9.3. Pharmacological Treatment for Stage C HFrEF: Soluble Guanylyl Cyclase Stimulators

Recommendation for Pharmacological Treatment for Stage C HFrEF: Soluble Guanylyl Cyclase Stimulators Referenced studies that support the recommendation are summarized in the Online Data Supplements.		
COR	**LOE**	**Recommendation**
2b	**B-R**	1. 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.[1]

Synopsis

In patients with progression of HFrEF despite GDMT, there may be a role for novel therapeutic agents. Oral soluble guanylyl cyclase stimulator (eg, vericiguat) directly binds and stimulates sGC and increases cGMP production. cGMP has several potentially beneficial effects in patients with HF, including vasodilation, improvement in endothelial function, as well as decrease in fibrosis and remodeling of the heart.[2–7] The VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial randomized 5050 higher-risk patients with worsening HFrEF to vericiguat versus placebo.[1]

Recommendation-Specific Supportive Text

1. Patients with HFrEF in the VICTORIA trial had LVEF <45%, NYHA class II to IV, were on GDMT, with elevated natriuretic peptides (BNP ≥300 pg/mL or NT-proBNP ≥1000 pg/mL if in sinus rhythm; higher cutoffs with AF), and recent HF worsening (hospitalized within 6 months or recently received intravenous diuretic therapy without hospitalization). Patients on long-acting nitrates, with SBP <100 mm Hg, or eGFR <15 mL/min/1.73 m^2 were excluded.[1] Over a median follow-up of 10.8 months, the primary outcome, cardiovascular death or HF hospitalization, occurred in 35.5% with vericiguat compared with 38.5% with placebo (HR, 0.90; *P*=0.019). All-cause mortality occurred in 20.3% in the vericiguat group and 21.2% in the placebo group (HR, 0.95; 95% CI, 0.84-1.07; *P*=0.38) and composite of any-cause death or HF hospitalization was also lower in the vericiguat group versus placebo group (HR, 0.90; 95% CI, 0.83–0.98; *P*=0.02). The relative risk reduction of 10% in the primary outcome was lower than expected, even in a higher risk population. Although not statistically significant, symptomatic hypotension (9.1% versus 7.9%; *P*=0.12) and syncope (4.0% versus 3.5%; *P*=0.30) were numerically higher in the vericiguat group versus placebo. There was heterogeneity by subgroup analysis, and patients in the highest quartile of NT-proBNP subgroup (NT proBNP level >5314 pg/mL) did not have benefit from vericiguat when compared with placebo.

7.2. Diuretics and Decongestion Strategies in Patients With HF

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7.3.1. Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi

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