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# Heart failure with reduced ejection fraction: What's new in the 2022 guideline?

## ABSTRACT

The 2022 guideline from the American College of Cardiology, American Heart Association, and Heart Failure Society of America provides practical recommendations for preventing, diagnosing, and managing patients with heart failure. This article summarizes the most important of these recommendations, specifically for managing patients with heart failure with reduced ejection fraction (HFrEF), and how they should change daily practice.

## KEY POINTS

- Optimal guideline-directed medical therapy for HFrEF comprises the combination drug containing the neprilysin inhibitor sacubitril and the angiotensin II receptor blocker (ARB) valsartan; an evidence-based beta-blocker; a mineralocorticoid antagonist; and a sodium-glucose cotransporter 2 inhibitor.
- Sacubitril-valsartan is preferred over angiotensin-converting enzyme (ACE) inhibitors and ARBs based on evidence from randomized controlled trials that it increases survival rates and reduces hospitalizations in patients with HFrEF. ACE inhibitors should be used only in patients who cannot tolerate sacubitril-valsartan, and ARBs used only in those who cannot receive sacubitril-valsartan or an ACE inhibitor.
- Patients with HFrEF receiving guideline-directed medical therapy whose ejection fraction increases to more than 40% should continue to receive guideline-directed medical therapy.

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Heart failure is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood. It can be classified in several ways, eg, by stage, effect of symptoms on function, and ejection fraction (**Table 1**). These classification schemes are important because the underlying causes, clinical trajectories, and effective therapies differ depending on these factors.

Stage C heart failure, in which patients develop symptoms of heart failure, requires the greatest focus and attention because these patients have high morbidity and mortality rates. In addition, for stage C heart failure with reduced ejection fraction (HFrEF) in particular, there is a wealth of evidence-based and guideline-based medical therapy to help patients feel better, stay out of the hospital, live longer, and potentially improve left ventricular function. Thus, stage C HFrEF and the 2022 guideline for treating it[1] will be the focus of this article.

## WHO WROTE THE GUIDELINE?

The 2022 guideline was developed by the American College of Cardiology, American Heart Association, and Heart Failure Society of America. It provides updated evidence-based recommendations[1] and supersedes the 2013 full guidelines[2] and the 2016[3] and 2017[4] focused updates.

**TABLE 1**
**Classifications of heart failure**

**Stages**

**A** At risk of heart failure due to conditions such as hypertension, diabetes, coronary artery disease
**B** Pre-heart failure with no symptoms but evidence for structural heart disease including reduced ejection fraction, increased left ventricular wall thickness, valvular disease
**C** Symptomatic heart failure with structural heart disease and heart failure symptoms
**D** Advanced heart failure with marked symptoms despite attempts at optimization of guideline-directed medical therapy

**New York Heart Association symptom classes**

**I** No symptoms
**II** Symptoms with moderate exertion
**III** Symptoms with mild exertion
**IV** Symptoms with minimal exertion or at rest

**Ejection fraction categories**

Reduced: ≤ 40%
Mildly reduced: 41%–49%
Preserved: ≥ 50%
Improved: > 40% after initially being ≤ 40%

### Classes of recommendation

The recommendations all receive a class (strength) of recommendation based on evidence from randomized controlled trials, nonrandomized analyses, and expert opinion. The recommendation classes are as follows:

- Class 1. Strong: there is evidence or general agreement that a given treatment or procedure is beneficial, useful, or effective.
- Class 2a. Moderate: the weight of evidence favors the treatment's usefulness or utility.
- Class 2b. Weak: the treatment's usefulness or efficacy is less well established by evidence or opinion.
- Class 3. No benefit: there is evidence or general agreement that the treatment or procedure is not useful or effective and in some cases may be harmful.

Class 1 and class 2a recommendations should be incorporated into clinical practice.

## WHAT ARE THE MAIN RECOMMENDATIONS?

The 2022 guideline is 159 pages long (including 40 pages of references) and contains 14 sections, 33 tables, 15 figures, and 192 recommendations. Specifically for stage C HFrEF, the high-yield recommendations include the following[5]:

**Sacubitril-valsartan** is recommended in patients with HFrEF and New York Heart Association (NYHA) class II or III symptoms to reduce morbidity and mortality (class 1 recommendation).

Even if a patient with chronic HFrEF and class II or III symptoms is already receiving an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) and tolerating it well, replacing it with sacubitril-valsartan is recommended to further reduce morbidity and mortality (class 1 recommendation).

**Beta-blockers**. In patients with HFrEF with current or previous symptoms, use of 1 of the 3 beta-blockers proven to reduce mortality risk (bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended to reduce mortality risk and hospitalizations (class 1 recommendation).

**Mineralocorticoid antagonists**. In patients with HFrEF and class II to IV symptoms, a mineralocorticoid antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if the estimated glomerular filtration rate is higher than 30 mL/min/1.73 $m^2$ and the serum potassium level is less than 5.0 mmol/L. Serum potassium, renal function, and diuretic dosing should be carefully monitored at initiation and every 3 to 6 months thereafter to minimize the risks of hyperkalemia and renal insufficiency (class 1 recommendation).

**Sodium-glucose cotransporter 2 (SGLT-2) inhibitors** are recommended in patients with symptomatic chronic HFrEF to reduce hospitalizations for heart failure and cardiovascular mortality, regardless of whether the patient has type 2 diabetes (class 1 recommendation).

**If the ejection fraction improves after treatment**, guideline-directed medical therapy should be continued to prevent relapse of heart failure and left ventricular dysfunction, even in patients who no longer have symptoms (class 1 recommendation).

**For patients self-identified as Black** with class III or IV symptomatic HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality (class 1 recommendation).

**Ivabradine**. For patients with symptomatic (class II to III) stable chronic HFrEF (left ventricular ejection fraction ≤ 35%) who are receiving guideline-directed medical therapy including a beta-blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of at least 70 beats per minute at rest, the addition of ivabradine (which inhibits the "funny" current of the sinoatrial node, reducing heart rate without reducing contractility) can be beneficial to reduce heart failure hospitalizations and cardiovascular death (class 2a recommendation).

## WHAT IS DIFFERENT FROM PREVIOUS GUIDELINES?

### Sacubitril-valsartan instead of ACE inhibitors and ARBs

The role of ACE inhibitors in HFrEF was established in the 1980s in patients with NYHA class IV heart failure,[6] with subsequent trials demonstrating their superiority over isosorbide dinitrate-hydralazine[7] and in less-sick patients with NYHA class I, II, or III symptoms.[8,9] ACE inhibitors became a cornerstone of HFrEF management in the late 1980s.

And they still would be, were it not for recognition of the importance of another important neurohormonal axis in heart failure, ie, the natriuretic peptide system, which promotes natriuresis, diuresis, and vasodilation—all good things.

While the now-defunct recombinant natriuretic peptide nesiritide offered no benefit in HFrEF,[10] another way to increase natriuretic peptide levels is by inhibiting their degradation by neprilysin. Sacubitril inhibits neprilysin, but it also increases angiotensin, so it had to be combined with an inhibitor of the renin-angiotensin system. While an ACE inhibitor would be the preferred choice for this job, the combination of sacubitril and an ACE inhibitor, both of which also increase bradykinin by inhibiting its degradation, would pose a prohibitive risk of angioedema,[11] which is why sacubitril is combined with valsartan, an ARB.

This theoretical benefit was tested in a randomized trial pitting sacubitril-valsartan against enalapril.[12] In this trial, 93% of patients were on beta-blockers, and 55% were on mineralocorticoid antagonists. The publication of this trial in 2014 marked the end of the reign of ACE inhibitors: compared with enalapril, sacubitril-valsartan demonstrated greater reduction in cardiovascular death and heart failure hospitalization. At a median of 27 months, when the trial was stopped early because of benefit, this combined end point had occurred in 26.5% in the enalapril group vs 21.8% in the sacubitril-valsartan group (hazard ratio 0.80, 95% confidence interval 0.73–0.87, $P < .001$).[12] This translates to a number needed to treat of 21 patients for 27 months to prevent 1 death or heart failure hospitalization.

The 2022 guideline reflects these advances, providing a class 1 recommendation for sacubitril-valsartan over an ACE inhibitor or ARB in patients with chronic symptomatic HFrEF.

### SGLT-2 inhibitors get a class 1 indication in HFrEF

In 2008, the US Food and Drug Administration announced that, to be approved, any new therapy for type 2 diabetes must demonstrate cardiovascular safety.[13] Subsequently, multiple medications in the new class of SGLT-2 inhibitors were run through the gauntlet of cardiovascular outcome trials. It was an unexpected boon when, between 2015 and 2020, multiple SGLT-2 inhibitors were deemed not only safe but also effective in reducing atherosclerotic events and—even more unexpectedly—heart failure.[14–17]

The world was therefore ready when in 2019 dapagliflozin was found to decrease the incidence of cardiovascular death and heart failure hospitalization in patients with HFrEF without diabetes.[18] Good news soon followed from empagliflozin in 2020.[19] The 2022 guideline emphasizes the significant impact of SGLT-2 inhibition in heart failure, giving this class of drugs a class 1 indication in HFrEF in patients with or without type 2 diabetes.

### The importance of comprehensive guideline-directed medical therapy

The 2022 guideline also highlights the importance of comprehensive guideline-directed medical therapy for HFrEF with sacubitril-valsartan, an evidence-based beta-blocker, a mineralocorticoid antagonist, and an SGLT-2 inhibitor. Use of all 4 drug classes is estimated to reduce all-cause mortality in HFrEF by 73% compared with no treatment, and over 2 years, the number needed to treat would be 3.9 patients to prevent

1 death or heart failure hospitalization.[20] Furthermore, an estimated 6.3 years of life is saved with use of all 4 drugs compared with just 2 (an ACE inhibitor and a beta-blocker) in patients ages 55 to 65.[21]

The 2022 guideline includes value statements created for select recommendations where high-quality, cost-effectiveness studies of the intervention have been published. Interventions with high value include treatment with sacubitril-valsartan instead of an ACE inhibitor as well as treatment with an evidence-based beta-blocker and mineralocorticoid in all patients with HFrEF. Treatment with an SGLT-2 inhibitor was deemed of intermediate economic value with a projection of high economic value if drug costs were reduced.

### Don't stop if ejection fraction improves

Heart failure with improved ejection fraction is a recently defined[22] and clinically meaningful category of heart failure. Whether patients whose ejection fraction improves while receiving guideline-directed medical therapy should keep receiving it was not clear until a landmark trial randomized such patients to continue or stop.[23] In this trial, heart failure recurred only in those patients in whom guideline-directed medical therapy was withdrawn.

**With adjunctive therapies, it is essential to avoid "indication creep," the inappropriate application of therapies to unproven uses**

There is now a class 1 recommendation that patients with heart failure with improved ejection fraction after treatment should continue guideline-directed medical therapy to prevent relapse of heart failure and left ventricular dysfunction, even patients whose symptoms have gone away.[1]

### Complementary therapies

**Isosorbide dinitrate-hydralazine.** In the 1980s, to assess whether the hemodynamic benefit of afterload translates into clinical benefit, a number of trials of vasodilatory therapy were done in patients with HFrEF. In 1986, a randomized trial demonstrated that prazosin was no better than placebo. The mortality rate was numerically lower with isosorbide dinitrate-hydralazine than with placebo, but the difference was not quite statistically significant ($P = .053$).[24]

While isosorbide dinitrate-hydralazine was ultimately bested by ACE inhibitors,[7] a subgroup analysis demonstrated significant benefit in patients who self-described as Black.[25] This hypothesis-generating signal was later confirmed: Black patients with HFrEF and NYHA class III or IV symptoms had higher survival rates with isosorbide dinitrate-hydralazine compared with placebo.[26]

With adjunctive therapies, it is essential to avoid "indication creep," the inappropriate application of therapies to unproven uses. For example, approximately 90% of enrolled patients in this trial were on ACE inhibitors and 70% were on beta-blockers. Thus, isosorbide dinitrate-hydralazine is not a substitute for optimal quadruple therapy in patients with HFrEF, but as adjunctive therapy in Black patients with blood pressure high enough to tolerate isosorbide dinitrate-hydralazine after initiation and optimization of guideline-directed medical therapy.

**Ivabradine.** Observational studies of patients with HFrEF noted an inverse relationship between heart rate and survival, with higher survival rates in patients with lower heart rates.[27] A meta-analysis of the randomized trials of beta-blockers in HFrEF also noted that those patients with greater lowering of heart rate had better survival.[28] Of course, these observations could be association (patients with lower heart rate and able to tolerate higher-dose beta-blocker treatment are less sick) rather than causation (patients with heart failure do better if they have a lower heart rate).

The medication ivabradine offered the possibility to assess the impact of heart-rate-lowering in HFrEF. By inhibiting $I_f$ (the funny current in the sinoatrial node), ivabradine reduces heart rate without reducing contractility, thus theoretically allowing greater heart-rate-lowering without the limiting hypotension and fatigue of beta-blockers.

A randomized trial tested this theory, assessing the impact of ivabradine in patients with HFrEF and a baseline heart rate of 70 beats per minute or more despite taking a beta-blocker at the highest dose they could tolerate.[29] The incidence of the primary end point (cardiovascular death or hospital admission for worsening heart failure) was 24% in the ivabradine group and 29% in the placebo group ($P < .0001$).[29]

However, it is important to avoid another potential indication creep: ivabradine is not a substitute for a beta-blocker. It has not been tested and found, by itself, to reduce the mortality rate, whereas beta-blockers have. Rather, ivabradine is an adjunctive therapy, to be added to the regimen in those who have a heart rate 70 beats per minute or more despite maximum-tolerated evidence-based beta-blocker therapy.

## DO OTHER SOCIETIES AGREE OR DISAGREE?

The 2016 European Society of Cardiology guideline for the diagnosis and treatment of acute and chronic heart failure[30] offers congruent recommendations regarding optimal guideline-directed medical therapy for stage C HFrEF, including the superiority of sacubitril-valsartan over ACE inhibitors and ARBs and the need for evidence-based beta-blocker, mineralocorticoid antagonist, and SGLT-2 inhibitor therapy. Recommendations for selective use of isosorbide dinitrate-hydralazine and ivabradine are also similar.

## HOW WILL THIS CHANGE DAILY PRACTICE?

The 2022 guideline emphasizes the benefit of "quadruple therapy" in patients with symptomatic HFrEF, ie, sacubitril-valsartan, an evidenced-based beta-blocker, a mineralocorticoid antagonist, and an SGLT-2 inhibitor. In clinical practice, it is essential to implement these guidelines in every patient at every visit with a stepwise approach:

**Step 1.** Is the patient on optimal guideline-directed medical therapy?

**Step 2.** If not, justify why (prior intolerance, cost, allergy) and document it.

**Step 3.** Is the patient on maximum-tolerated dosages of guideline-directed medical therapy?

**Step 4.** If not, either increase dosages in a stepwise fashion, or document why further titration is not possible (limiting heart rate, blood pressure, potassium, or creatinine). This would include stepwise initiation, every 1 to 2 weeks, of the following:

- Low-dose sacubitril-valsartan (sacubitril 24 mg and valsartan 26 mg, twice daily), followed by
- A beta-blocker (carvedilol 3.125 twice daily or metoprolol succinate 25 mg daily), then
- A mineralocorticoid antagonist (spironolactone 25 mg daily or eplerenone 50 mg daily), and
- An SGLT-2 inhibitor (dapagliflozin 10 mg daily or empagliflozin 10 mg daily).

After all 4 pillars of treatment are initiated, then sacubitril-valsartan and beta-blocker could be doubled every 1 to 2 weeks as tolerated by heart rate, blood pressure, and serum potassium and creatinine levels.

## WHEN WOULD THE GUIDELINES NOT APPLY?

While optimal guideline-directed medical therapy will improve quality of life and survival of patients with HFrEF, there are important populations in whom these therapies are not indicated.

First, ensure that patients are receiving optimal quadruple therapy at maximum-tolerated doses before initiating isosorbide dinitrate-hydralazine or ivabradine (avoid the indication creep described above).

Next, be mindful of the following specific contraindications:

- Sacubitril-valsartan is contraindicated in patients with any history of angioedema, particularly in reaction to an ACE inhibitor.
- Mineralocorticoid antagonists should not be prescribed in patients with an estimated glomerular filtration rate less than 30 mL/min/1.73 $m^2$ or a serum potassium level higher than 5.0 mmol/L, as these medications could increase the risk of hyperkalemia hospitalizations and deaths in such patients.[31]
- SGLT-2 inhibitors are contraindicated in patients with type 1 diabetes mellitus or on dialysis.
- Finally, according to the 2022 guideline, ivabradine is not recommended in patients with atrial fibrillation, as it increases the risk of atrial fibrillation.

## DISCLOSURES

The author reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

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