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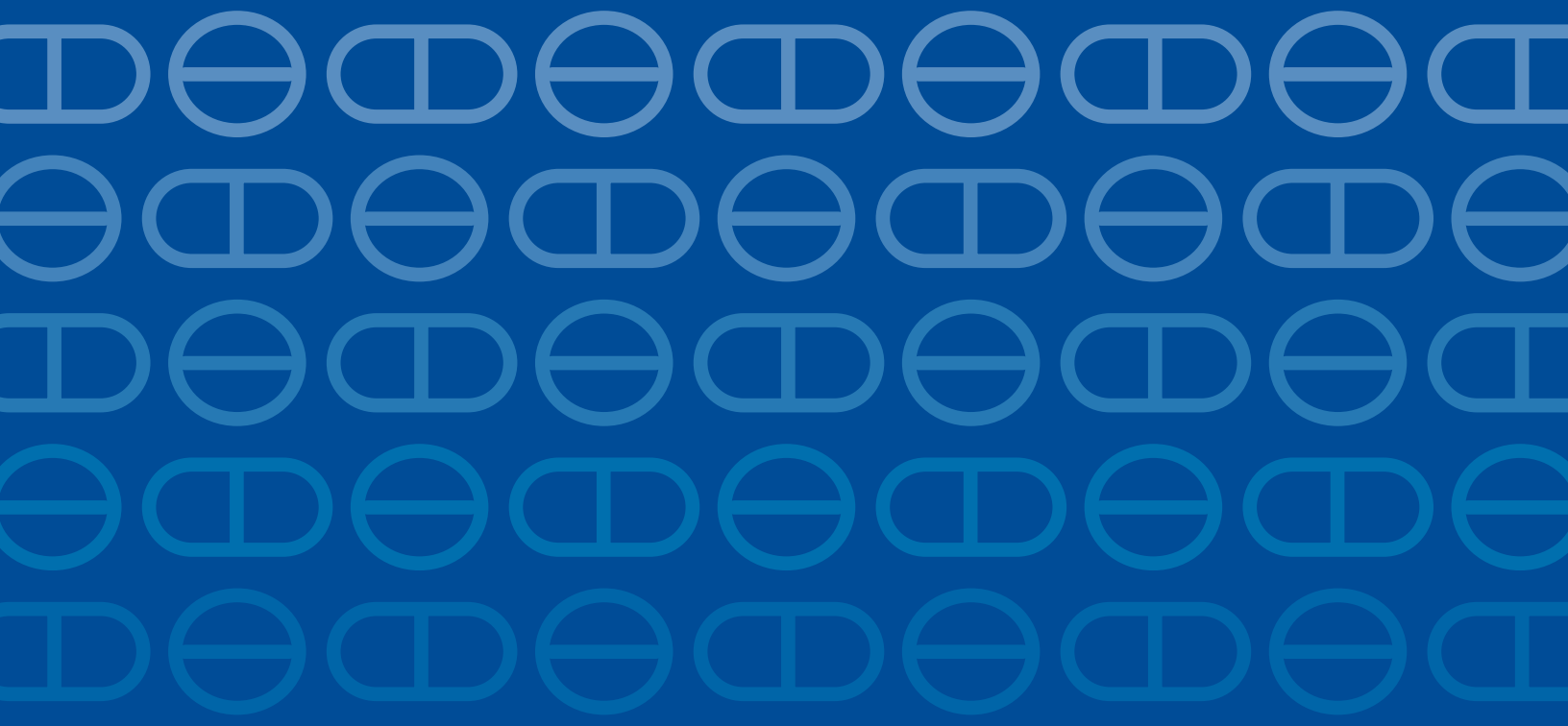
Heart failure

Improving outcomes in primary care



Heart failure: improving outcomes in primary care

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

Alosa Health

Heart failure: improving outcomes in primary care

Accreditation:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education and American Nurses Credentialing Center through the joint providership of Harvard Medical School and Alosa Health. The Harvard Medical School is accredited by the ACCME to provide continuing medical education for physicians and the ANCC to provide CNE credit hours to nurses.

Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 1.00 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This continuing nursing education activity was approved by ANA Massachusetts, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. This activity was approved for 1.00 contact hours, of which 0.25 is eligible for pharmacology credit. Contact hours are awarded commensurate with participation and completion of the online evaluation and attendance attestation.

Activity Overview:

The goal of the educational program is to provide primary care clinicians with a review of evidence-based practices for the evaluation and management of heart failure in primary care settings, including summaries of recent changes to HF treatment guidelines.

The education program has several components, which include:

1. Written evidence report (print monograph)
2. Summary document of 4-5 key messages
3. “Academic detailing” educational sessions with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
4. Reference cards for easy access to key materials
5. Patient education information (brochure/tear off sheets)

Its goal is to critically review and synthesize the most current clinical information on these topics into accessible, non-commercial, evidence-based educational material, to be taught interactively to providers by specially trained clinical educators.

Target Audience:

The educational program is designed for physicians practicing internal medicine, primary care, family medicine, and geriatrics, and nurses and other health care professionals who deliver primary care.

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Identify risk factors for heart failure (HF) such as hypertension, diabetes, and atrial fibrillation and treat them to prevent or delay the development of HF.

- Discuss the use of non-pharmacologic strategies such as sodium and fluid restriction, patient education, and exercise as possible strategies to improve quality of life and adherence to medications.
- Describe the four recommended medication classes used for patients with reduced ejection fraction (EF): angiotensin system blockers, beta-blockers, and aldosterone antagonists, as well as SGLT-2 inhibitors.
- Summarize the management strategy for patients with HF with preserved EF, such as to treat hypertension and volume overload with diuretics, and prescribe an ARNI, an aldosterone antagonist, or an SGLT-2 inhibitor depending on patient's EF.
- After HF hospitalization, reiterate the importance of medication adherence, review weight goals, and reinforce salt or fluid restriction.
- Employ goals of care discussions and encourage the use of advance directives for patients with severe, end-stage HF.

Disclosure Policy:

Harvard Medical School has long held the standard that its continuing medical education courses be free of commercial bias.

In accord with the disclosure policy of the Medical School as well as standards set forth by the Accreditation Council for Continuing Medical Education, course planners, speakers, and content reviewers have been asked to disclose any relevant relationship they, or their spouse or partner, have to companies producing, marketing, re-selling or distributing health care goods or services consumed by, or used on, patients. In addition, faculty have been asked to list any off-label uses of pharmaceuticals and/or devices for investigational or non-FDA approved purposes that they plan to discuss. Such disclosure is not intended to suggest or condone bias in any presentation, but is elicited to provide the course director and participants with information that might be of potential importance to their evaluation of a given presentation.

Disclosures:

This material is provided by Alosa Health, a nonprofit organization which is not affiliated with any pharmaceutical company. No commercial support has been received for this activity. All individuals including planners, authors, reviewers, academic detailers, staff, etc., who are in a position to control the content of this educational activity have, on behalf of themselves and their spouse or partner, reported any financial relationships related to the content of this activity. The Independent Drug Information Service (IDIS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.

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Setting the stage

Heart failure (HF) is a complex clinical syndrome resulting from any structural or functional impairment of ventricular filling or the ejection of blood.[1] HF means the heart can't pump enough blood to meet the body's metabolic demands, or that it can do so only at the expense of elevated intracardiac filling pressures. Although HF and the symptoms it causes vary in severity across patients, HF can be classified in terms of the ejection fraction (EF): the amount of blood pumped out of the left ventricle with each cardiac cycle divided by the total amount of blood in the ventricle at the end of diastole. The point at which EF is considered "preserved" or "reduced" is not absolute, although an EF of ≥55% is often considered "normal." Some clinical trials have defined "reduced" EF as ≤40% or ≤35%. Other trials have defined "preserved" EF as anywhere between >40% and >55%.[1]

In this document the terms "heart failure with reduced ejection fraction" (HFrEF) and "heart failure with preserved ejection fraction" (HFpEF) will be used, with HFrEF defined as EF ≤40% and HFpEF defined as EF ≥50% (Table 1). Morbidity and mortality rates for the two types are similar, with 1-year hospital admission rates of about 50% and 1-year mortality rates of approximately 22-29%.[2] As shown in Table 1, patients with EF >40% can fall into the "borderline" or "improved" subcategories of HFpEF.

Table 1: Heart failure classifications[3]

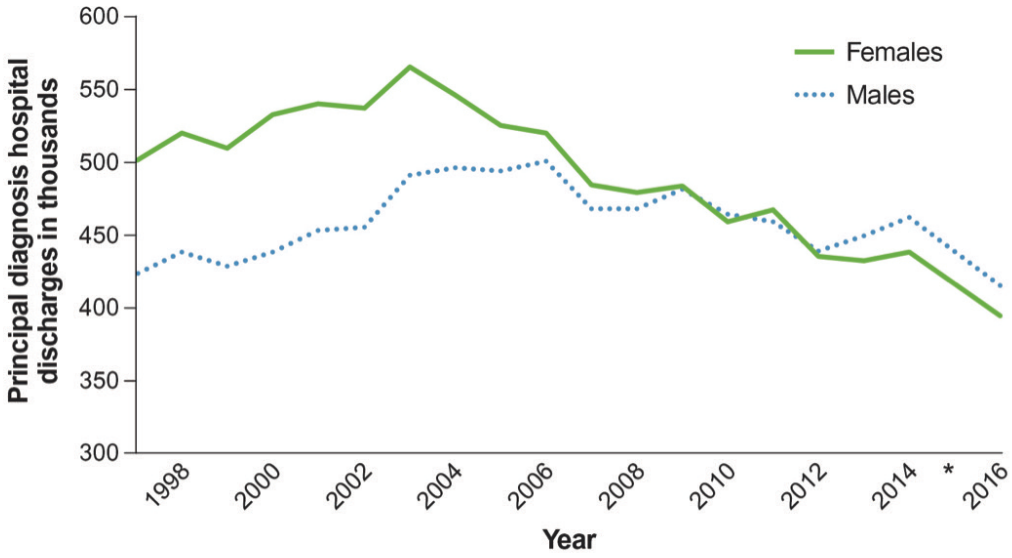
Classification	EF (%)	Description
Heart failure with reduced ejection fraction (HFrEF)	≤40%	Also referred to as **systolic** HF.
Heart failure with preserved ejection fraction (HFpEF)	≥50%	Also referred to as **diastolic** HF.
HFpEF, borderline	41-49%	Characteristics, treatment patterns, and outcomes similar to patients with HFpEF.
HFpEF, improved	>40%	Patients with baseline EF <40% but with a ≥10% increase from baseline to >40%.
Note: it is important to consider the trajectory of EF over time in addition to EF at any point in time.		

Although the morbidity and mortality associated with HF are high, the appropriate use of evidence-based treatments can prolong life and improve its quality. This module reviews evidence-based practices for the evaluation and management of HF in primary care settings, including summaries of recent changes to HF treatment guidelines.

Epidemiology

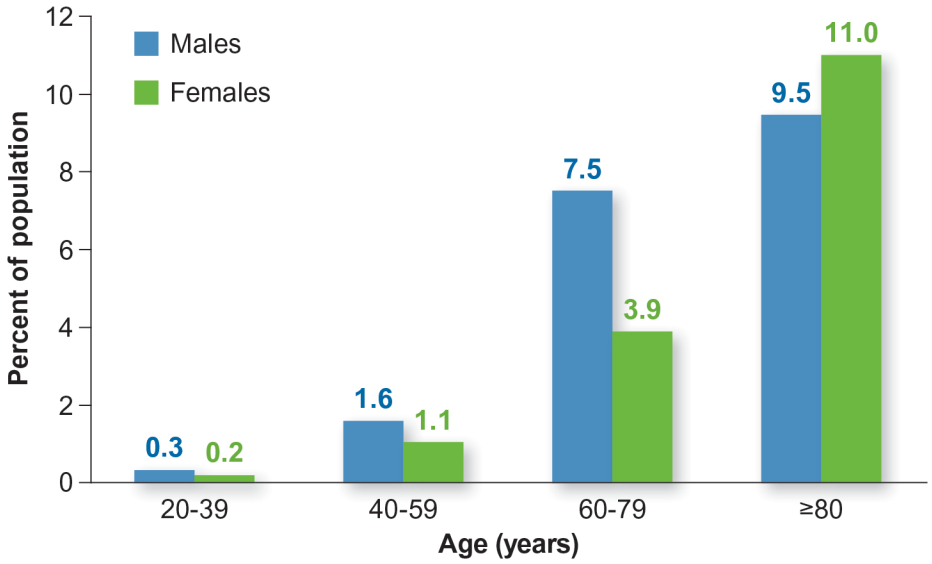
Although rates of HF hospitalization have declined in the past two decades (Figure 1), HF remains a major cause of morbidity and mortality, affecting about 6 million people in the U.S., with that number expected to rise to 8 million by 2030.[4] Approximately 825,000 new cases of HF are diagnosed each year, and prevalence rises steeply with age.[5] After age 45 the lifetime risk of developing HF ranges from 20%-45%.[4] Figure 2 shows representative prevalence rates by age and sex.

Figure 1: Heart failure remains a leading cause of hospital admission in older adults



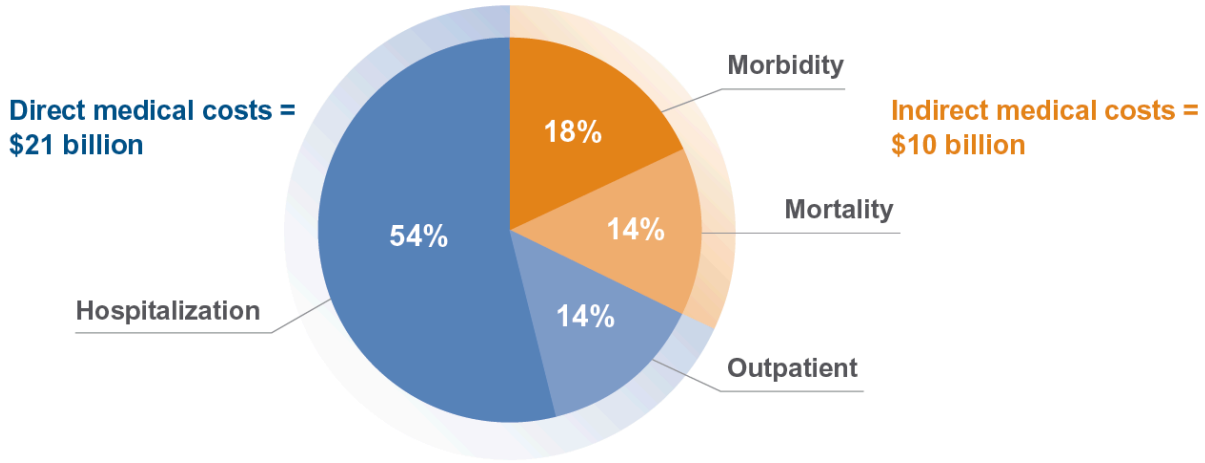
*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the International Classification of Diseases. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

Figure 2: HF prevalence[4]



HF is associated with high mortality: about 20% of people with symptomatic HF die within a year of diagnosis, about half die within 5 years of diagnosis, and up to 75% die within 5 years of hospitalization for HF.[6,7] In general, life expectancy is greater among women with HF compared to men with HF.[8] About 20% of patients hospitalized for HF will be readmitted within 30 days.[9] Medical expenditures related to HF in the U.S. were about $31 billion in 2012 (Figure 3), a figure expected to rise to $70 billion by 2030.[10,11]

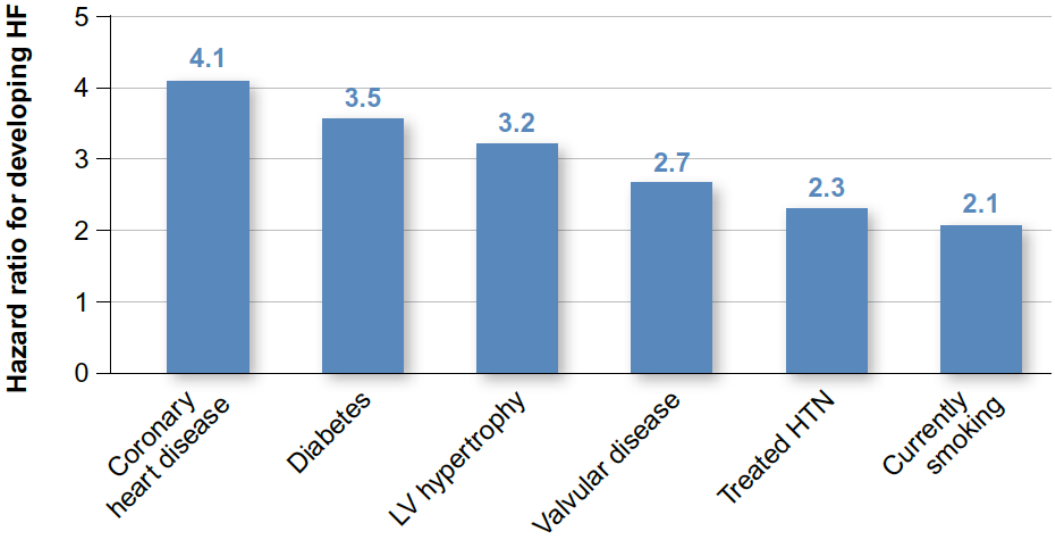
Figure 3: Medical costs associated with heart failure[10,11]



Risk factors and associated conditions

Coronary heart disease is the largest risk factor for HF (with risk higher in men than in women), although diabetes and several other conditions also confer significant risk (Figure 4). The lifetime risk of HF is doubled for patients with hypertension compared to normotensive adults.[12]

Figure 4: Risk factors for developing heart failure[13]



HF is also causally associated with a wide range of conditions, summarized in Table 2.

Table 2: Conditions associated with, or contributing causally to, HF

Primary cardiovascular disease • dilated/familial cardiomyopathy • hypertrophic/ restrictive cardiomyopathy • valvular dysfunction • myocarditis/ pericarditis • ischemic heart disease	**Primary pulmonary disease** • pulmonary hypertension • COPD • obstructive sleep apnea
Toxin related • alcohol • cocaine • chemotherapy (e.g., doxorubicin, trastuzumab)	**Infiltrative disease** • amyloid cardiomyopathy • cardiac sarcoid • glycogen storage diseases
Endocrinopathies • thyroid disease • acromegaly/GH deficiency	**Other** • lupus/ rheumatoid arthritis • HIV • peripartum • stress-induced

One relatively under-recognized contributing factor for HF (particularly HFpEF) is amyloid cardiomyopathy (ACM), which results from myocardial deposition of light chains or misfolded proteins such as transthyretin (TTR) or pre-albumin.[14] TTR cardiac amyloidosis is unrelated to plasma cell dyscrasia and is more common than previously recognized, affecting 10%-15% of older adults with HFpEF.[14] Diagnostic clues include: peripheral and autonomic neuropathy; biceps tendon rupture; carpal tunnel syndrome; lumbar stenosis, macroglossia and, in the case of light chain ACM, nephrotic syndrome. Characteristic patterns on echocardiography and cardiac MRI may strongly suggest the disease but are not diagnostic. Signs of ACM on ECG include low voltage, pseudoinfarct pattern, conduction abnormalities, and atrial arrhythmias. Signs on transthoracic echo include ventricular hypertrophy, biatrial enlargement, and apical sparing pattern on strain imaging.

Early recognition of ACM is important because patients with this disease should avoid dihydropyridine calcium channel blockers, beta blockers, or digoxin and because these patients should be referred to a cardiologist for further evaluation and consideration of disease-modifying therapies.[14] In addition, it is important to exclude light chain ACM in any patient with suspected ACM by means of serum protein electrophoresis with immunofixation, urine protein electrophoresis, and serum free light chain tests. Patients with light chain ACM should be urgently referred to a hematologist/oncologist for treatment (e.g., chemotherapy, stem cell transplant).

BOTTOM LINE: Coronary heart disease is the largest risk factor for HF (with risk higher in men than in women), although diabetes and several other conditions also confer significant risk. Amyloid cardiomyopathy is increasingly recognized as a significant contributor to HFpEF and should be investigated as a possibility when HFpEF is diagnosed.

Diagnosis and evaluation

HFrEF and HFpEF can be difficult to distinguish by history, physical exam, and on typical diagnostic tests such as ECG, chest x-ray, and laboratory testing. An echocardiogram (echo) is usually required to make a definitive diagnosis. Currently in the U.S. about half of HF cases are categorized as HFrEF and half as HFpEF. A diagnosis of HFpEF is usually made only after excluding non-cardiac causes for the patient's symptoms. The pathophysiology of HF can affect both the left and right ventricles; chronic left ventricular (LV) dysfunction with high LV filling pressures and chronically elevated pulmonary pressures may eventually lead to structural changes and right ventricular dysfunction. Isolated right ventricular HF is frequently associated with chronic lung disease (such as COPD, chronic pulmonary emboli, or pulmonary hypertension).

The general rule for HF diagnosis is that it should be based on symptoms and/or signs caused by structural or functional cardiac abnormality plus either objective evidence of cardiogenic pulmonary or systemic congestion or elevated brain natriuretic peptide (BNP) levels (see BNP section below for details).

Physical exam and history

Patients with symptoms of new HF should be interviewed about past and present symptoms, when symptoms occur, and how/when the symptoms started. They should be queried about present and past use of alcohol, drugs, or chemotherapy agents, all co-morbid conditions (e.g., ischemic heart disease, hypertension, obstructive sleep apnea, HIV, COPD) and family history of heart disease.

Table 3: Components of a focused HF history

Component
• Etiology of HF (cardiac and non-cardiac causes)
• 3-generation history (dilated cardiomyopathy)
• Symptoms — shortness of breath or shortness of breath when bending forward (i.e., bendopnea) — fatigue/exercise intolerance — coughing — signs of volume overload (e.g., lower extremity swelling, ascites, orthopnea, paroxysmal nocturnal dyspnea, weight gain) — chest pain — sleep problems (sleep apnea, orthopnea)
• Medications that can exacerbate HF (e.g., NSAIDs)
• Diet (e.g., sodium and fluid intake)
• Recent or frequent hospitalizations

The following physical exam findings are common in patients with HF, although no single finding is particularly sensitive or specific:[1]

- vital signs

    - tachycardia
    - weight gain
- jugular venous distension
- heart sounds
    - gallops (S3, S4)
    - murmurs suggest valvular heart disease
- pulmonary status
    - respiratory rate, rales
- hepatomegaly and/or ascites
- peripheral edema

Lab tests during the initial workup of patients with HF may help determine etiology, rule out other conditions, or help guide management, and should include:[15,16]

- complete blood count
- thyroid-stimulating hormone
- urinalysis
- fasting glucose and lipid profile
- urinalysis
- liver function tests (attention to gamma gap)
- blood urea nitrogen and serum creatinine
- serum electrolytes (including magnesium and calcium)

Other lab testing should only be done if the history or exam suggests an unusual cause of HF (such as Cushing's disease, HIV, or an infiltrative disease). Check cardiac biomarkers (troponin I or T) if acute ischemia is suspected.

Brain natriuretic peptide (BNP) testing

BNP is a natriuretic hormone released primarily from the heart. It is generated by myocytes in the presence of triggers such as myocardial "stretch" or other conditions. It can be measured in serum to help determine if symptoms, such as dyspnea, are due to HF (see Table 4). Two tests measure different sections of the same hormone: the BNP test and the N-terminal pro-BNP (NT-proBNP) test.

Care should be taken in interpreting BNP test results, however, because the levels of natriuretic peptides may be elevated by a wide range of cardiac and non-cardiac conditions (e.g., valvular heart disease, atrial fibrillation, anemia, renal failure, bacterial sepsis). Higher BNP values are typically seen in older adults, women, patients with CKD and patients with atrial fibrillation. Lower BNP levels may be seen in patients with obesity or pericardial disease.

Table 4: BNP and NT-proBNP diagnostic values[17,18]

BNP	
<100 pg/mL	unlikely HF
100-400 pg/mL	borderline
>400 pg/mL	suspect HF
NT-proBNP	
<300 pg/mL	unlikely HF
>450 pg/mL	suspect HF in patients <50 years
> 900 pg/mL	suspect HF in patients 50-75 years
>1800 pg/mL	suspect HF in patients >75 years

BNP testing may also help determine the prognosis of a HF patient. Elevated BNP levels are predictive of worse HF outcomes. In the **Val-HeFT trial** of 4300 patients with HFrEF, patients with the greatest percent decrease in BNP from baseline at 4 and 12 months had the lowest rates of morbidity and mortality, whereas patients with greatest percent increase in BNP had the highest morbidity and mortality.[19]

BNP-guided therapy may improve mortality in HFrEF patients <74 years old but the evidence is mixed.[20,21] In a meta-analysis of nine randomized controlled trials that included 2000 patients, mortality was reduced by 38% in the BNP-guided group compared to standard of care (relative risk 0.62; 95% CI: 0.45-0.86, p=0.004), although no benefit was seen in patients >75 years.[22] Importantly, patients in the BNP-guided group were more likely to achieve target doses of ACE inhibitors and beta-blockers.

On the other hand, the **GUIDE-IT trial**, which randomized 1100 patients with HFrEF to either BNP-guided strategy or usual care, was terminated early for futility.[23] No significant differences were observed between the groups in rates of cardiovascular death or HF hospitalization and both groups had similar reductions in BNP levels during follow-up.

Given the conflicting evidence, BNP-guided therapy may be helpful in some patients, but is not broadly recommended.[1]

Non-invasive testing

An ECG and echo are both routinely performed in patients with new or worsening HF signs/symptoms. An ECG is valuable in determining the heart rate and rhythm (which may affect management), the presence of left ventricular hypertrophy, abnormal conduction, or Q waves suggesting prior myocardial infarction. An echo is valuable for assessing a number of structural cardiac elements that can affect patient management, including the LVEF, diastolic function or dysfunction, chamber size, valvular abnormalities (stenosis or regurgitation), pericardial effusion, and estimated pulmonary artery pressure. Repeat an echo if there are changes in a patient's clinical status or after 3-6 months of guideline-directed medical therapy (GDMT) to inform decisions on primary prevention with an implantable cardioverter-defibrillator (ICD).

The chest X-ray can be valuable for ruling in or ruling out HF as the etiology of the patient's symptoms (the typical findings in HF include interstitial edema, vascular congestion, and pleural effusions).

Additional cardiac imaging should be performed only in selected patients and most often in conjunction with a cardiologist. Cardiac MRI is a good diagnostic test for suspected myocardial pathology (such as infiltrative diseases like sarcoidosis or amyloidosis) or pericardial pathology (such as pericarditis or constriction). Cardiac CT (with or without coronary CT angiogram) can detect cardiac vascular calcifications/stenosis, although the significance of these findings for management is not always clear and the testing carries the risks of radiation and contrast. A number of different types of cardiac nuclear perfusion scans can be performed if cardiac ischemia is suspected, the type of which will depend on locally available technology and cardiology preferences. These should be performed in patients whose HF etiology is not known after physical exam, laboratory testing, and ECG/echocardiography and/or if ischemia is suspected. Technetium pyrophosphate (PYP) nuclear scan is a sensitive and specific test for TTR cardiac amyloidosis.

Invasive testing

Further invasive testing for patients with new or worsening HF should be dictated by the suspicion of the etiology of the HF. For patients with suspected or confirmed cardiac ischemia, cardiac catheterization may be pursued for diagnostic and/or therapeutic purposes. For select patients with suspected myocarditis or myocardial infiltrative diseases, a myocardial biopsy may be appropriate.

Pulmonary disease work up

Patients with a history suggestive of obstructive sleep apnea (OSA) should be referred for a diagnostic sleep study, and for OSA management if results from polysomnography are positive. Pulmonary function tests should be ordered on those with symptoms of COPD (chronic cough or sputum production, especially in smokers or those exposed to second hand smoke). A workup for chronic thromboembolic disease may be undertaken for those with suspected (or history of) venous thromboembolic disease.

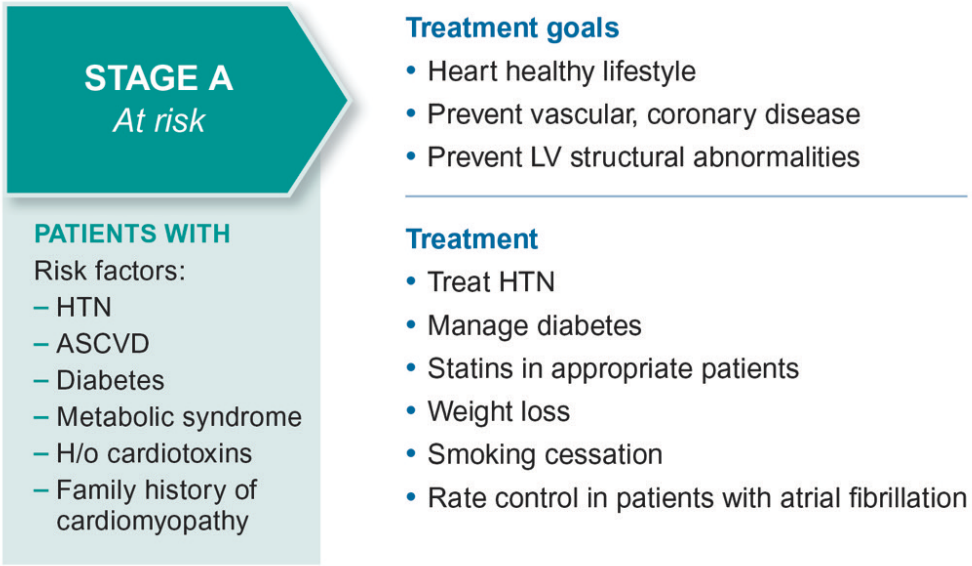
BOTTOM LINE: HF diagnosis should be based on symptoms and/or signs caused by structural or functional cardiac abnormality plus either objective evidence of cardiogenic pulmonary or systemic congestion or elevated BNP levels.

Overview of HF management in primary care

The details of managing HF (regardless of EF) are driven by a patient's HF stage, as outlined below. These are based on the ACCF/AHA/HFSA staging system, which describes a patient's progressive pathophysiological changes over time. This system tries to help clinicians focus on how HF develops over time and, accordingly, begins with Stage A, in which patients do not actually have HF, but have an increased risk of HF that can be reduced with treatment of their individual risk factors.

Stage A

Figure 5: Management of patients at risk for heart failure (stage A)[1]



Note that treating hypertension in Stage A patients, particularly in the elderly, may significantly lower the risk for HF. In the SPRINT trial (N=9,361) adults in the treatment arm had a 38% reduced risk of HF compared to those in the control arm (HR 0.62; 95% CI: 0.45-0.84).

Treating patients in Stage A who have diabetes with the sodium-glucose cotransporter 2 inhibitor (SGLT-2) dapagliflozin may lower the risk of HF. In the **DECLARE-TIMI 58 trial** (N=17,160) baseline prevalence of HF in the participants was 3.9% with HFrEF and 7.7% with HFpEF.[24] Dapagliflozin reduced the rates of hospitalization for HF in patients with no baseline HF (HR 0.77; 95% CI: 0.60-0.97) (Table 5). A non-significant reduction was observed in patients with HF but no reduced EF (HR 0.72; 95% CI: 0.50-1.04).

Table 5: Summary of dapagliflozin results in patients with diabetes without heart failure

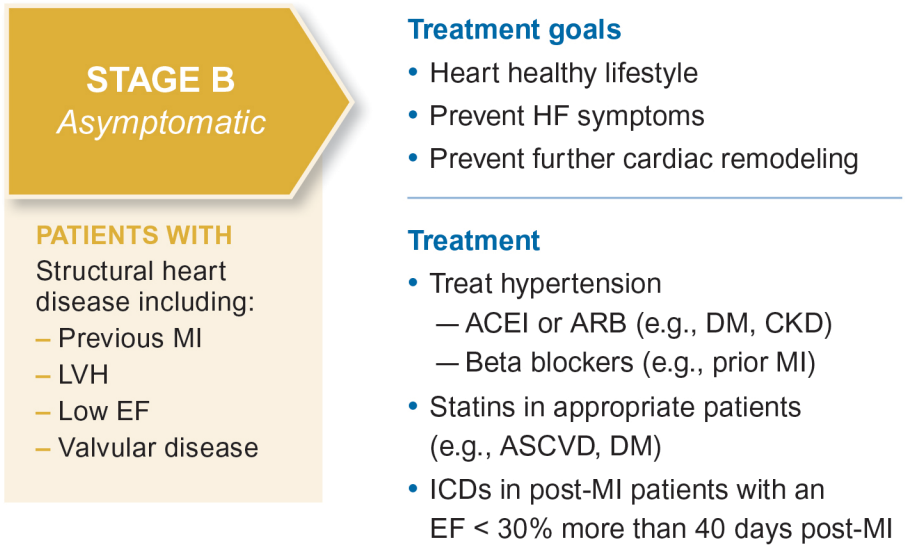
Outcome	Relative risk reduction	Hazard ratio (95% CI)
CV death and HF hospitalization	12%	0.88 (0.74-1.03)
HF hospitalization	23%	0.77 (0.60-0.97)
CV death	-	1.01 (0.81-1.25)
All-cause mortality	4%	0.96 (0.84-1.10)

Stage B

Stage B (Figure 6) includes patients who have developed structural heart disease but do not yet have HF symptoms. All patients with Stage B HF should be treated for hypertension, if needed, as well as with statins as appropriate. Patients with reduced EF should also be treated with a beta blocker and either an ACE inhibitor or an angiotensin receptor blocker (ARB). Non-dihydropyridine calcium channel blockers

(CCBs) should be avoided. Treatment of these patients can reduce or delay the development of HF symptoms. In patients with reduced EF and a prior myocardial infarction (MI), all of the above therapies should be used and an implantable cardioverter defibrillator (ICD) should be considered if the EF is <30% and the patients is more than 40 days post-MI.

Figure 6: Management for patients with Stage B heart failure



Stages C and D

Patients with symptomatic HF (Stages C & D) should be treated with appropriate evidence-based pharmacologic therapies, which will be detailed in sections below. For patients with reduced EF, devices such as ICDs and cardiac resynchronization therapy (CRT) may be appropriate.

Figure 7: Management for patients with stage C heart failure

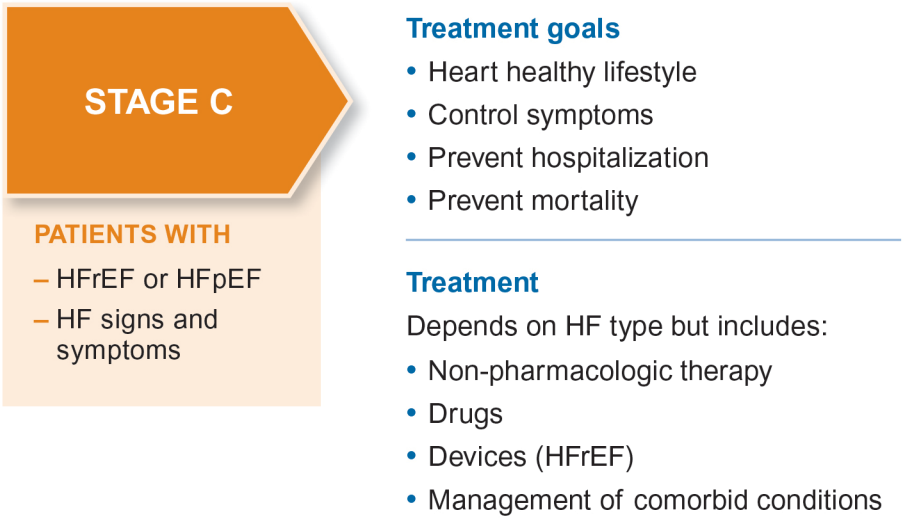
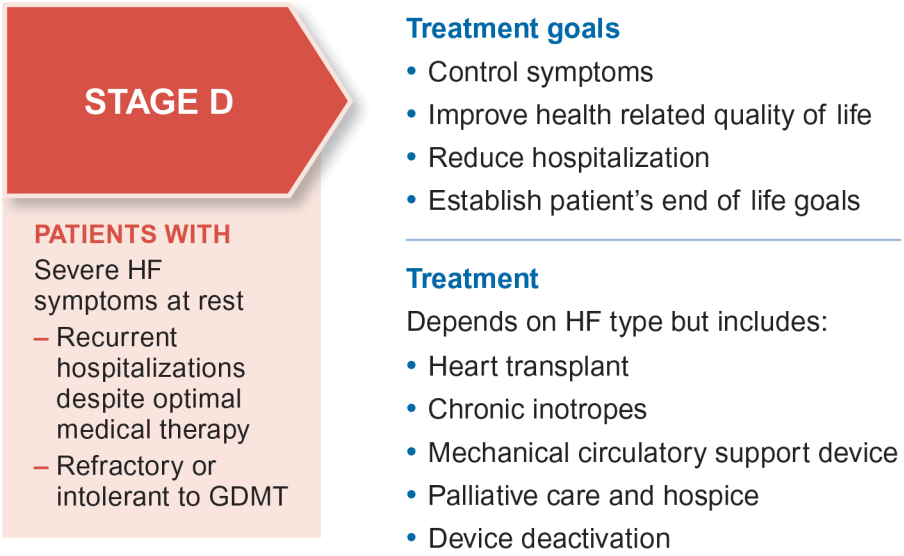


Figure 8: Management of patients with stage D heart failure



BOTTOM LINE: Treating hypertension and diabetes in Stage A patients can significantly lower the risk for HF. Patients in Stage B should be treated for hypertension and hyperlipidemia as appropriate. Patients with asymptomatic left ventricular systolic dysfunction (Stage B) should also be treated with a beta blocker and an ACE inhibitor or an ARB. Patients with symptomatic HF (Stages C & D) should be treated with evidence-based pharmacologic therapies, as appropriate.

Non-pharmacological management

Patient education about self-management

Managing HF is complicated for patients. They must learn about their medications, how to monitor their symptoms and weight, and how to make changes to their diet and activity levels. Educating, "coaching," and supporting patients is a continuing effort and is key to better outcomes because, among other things, medication nonadherence among patients with HFrEF is estimated at 20%-50%.[25] Education should be tailored to the patient's literacy level, cultural context, resources, and social support levels. Patients should be asked to demonstrate understanding of the concepts relevant to their management, by reiterating the elements in their own words. Difficulty in affording medications, getting transportation for appointments or to pick up medications, and any other barriers should be addressed. Support for dietary modifications and weight management from family and friends should be assessed.

Some interventions to improve education have been shown to increase knowledge, self-monitoring, and medication adherence, and to decrease hospital admissions.[1] Successful programs have the following components:

- longer-term involvement

- frequent contact
- medication management performed by a pharmacist or HF nurse
- use of multidisciplinary HF clinics

A meta-analysis of 771 trials evaluating interventions to improve medication adherence found that such interventions were associated with lower mortality (OR 0.89; 95% CI: 0.81-0.99) and lower rates of hospital readmission (OR 0.79; 95% CI: 0.71-0.89).[26] The most effective interventions were delivered face-to-face by pharmacists and were habit-based and behavior-targeted (rather than cognitive-focused).

The role of nurses in HF care

Nurses can play an important role in the provision of comprehensive HF care.[27] Nurses are well positioned to assess patient knowledge and to help overcome learning barriers by reinforcing and clarifying educational messages. A systematic review found that nurse-led education and follow up with patients, whether delivered over the phone or face-to-face, is associated with improved patient outcomes and lower hospitalization and readmission rates.[28] Nurses in community and primary care settings are an integral part of improving clinical and functional health outcomes in patients with HF, in collaboration with other healthcare professionals.

Telemonitoring

Many outpatient and hospital systems have instituted telemonitoring systems to remotely monitor and manage HF patients for physical signs (such as weight, vital signs, or urine output), symptoms (such as edema or shortness of breath), laboratory values (such as creatinine or BNP), and medication/dietary compliance (by self-report or by use of more sophisticated devices). The potential benefit of telemedicine programs is the early detection and management of disease deterioration. It is generally accomplished by the transmission of information to a clinician, who uses standard guidelines and operating procedures to direct the patient on how best to proceed. Regular telephone contact with the patient can prevent HF exacerbations and hospital admissions.[29] A systematic review of 56 articles found numerous outcome improvements in telemonitoring in randomized trials, although how effectively these improvements translate to real-world practice has not been as well-studied (Table 6).

Table 6: Efficacy of telemonitoring technologies in HF[29]

Type of telemonitoring modality	Outcomes improved in randomized trials
Device-based: Participants enter data into a device, which is transmitted to a monitoring station	Decreased mortality Decreased hospitalizations Decreased anxiety / depression scores Increased self-efficacy scores Increased exercise adherence Increased QOL
Telephone touch-pad-based: Participants enter data into a telephone, which is transmitted to a monitoring station	Decreased hospitalizations Decreased time to target beta blocker
Video consultation-based: Participants were monitored by video conferences by nurses	No improvements
Website-based: Participants enter data into a website, which was monitored by healthcare professionals	Decreased hospital days
Combinations	Decreased ED visits and charges Decreased readmission rates Decreased hospital days Decreased mortality Decreased cardiac claims (e.g., cost)

Sodium

Sodium restriction is routinely recommended in patients with symptomatic HF, although this is not based on clinical trials. Excess sodium intake commonly precipitates HF exacerbations and is a frequent cause of HF admissions. However, improvement in clinical outcomes with a reduced sodium diet has not been consistently demonstrated in studies. Recommendations for sodium intake for patients with symptomatic HF range from <2000 mg/day to <3000 mg/day.[30] A lower sodium diet has been shown to reduce blood pressure and cardiovascular events in patients with hypertension, therefore, for patients who are at risk of HF or have asymptomatic left ventricular systolic dysfunction, especially those with hypertension, a lower sodium diet is recommended.

ACCF/AHA HF Guidelines for sodium intake:[1]

- HF stages A and B: <1500 mg/day
- HF stages C and D: <3000 mg/day

Some patients with HF will also need to restrict their fluid intake. Limiting fluid intake to around 2 liters per day is usually needed for most hospitalized patients, however fluid restriction is less commonly used in ambulatory patients who are not diuretic resistant or significantly hyponatremic.[1]

Treatment for sleep apnea

A study of 108 patients with HF found that 61% had some form of sleep-disordered breathing (31% central apnea and 30% obstructive sleep apnea).[31] This may actually be a conservative estimate because HF patients are less likely to experience symptoms of daytime sleepiness, leading to under-diagnosis.[1] Apneic episodes can trigger the activation of sympathetic nervous system hormones that are detrimental to patients with HF, since they increase heart rate and blood pressure. Treatment of obstructive sleep apnea can improve cardiac function and symptoms. In a controlled trial, 258 patients with systolic HF (mean EF 25%) and sleep apnea were randomized to continuous positive airway pressure (CPAP) or no CPAP; the CPAP group had modest but significant increases in six minute walk tests (by about 20 meters) and ejection fraction (by about 2%), but there were no significant differences between the groups in HF hospitalizations or mortality.[32] A trial randomized 1,325 patients with HFrEF and central apnea to adaptive servo-ventilation (a relatively new type of positive airway pressure device) or control and found no significant difference in HF-related mortality or hospitalization, but all-cause and cardiovascular mortality were both increased with this therapy.[33]

Cardiac rehabilitation and exercise

HF patients often have limited exercise capacity, but most retain some physical abilities that can be enhanced gradually and carefully. Exercise training has been shown to improve exercise capacity and quality of life, to reduce HF hospitalizations, and prolong survival[34] and yet only about 10% of eligible patients with HF get a referral to cardiac rehabilitation at the time of discharge.[35] Cardiac rehabilitation that combines exercise, self-care education, and psychological support was shown to improve functioning and quality of life in elderly patients with HFrEF.[36] The 6-month study of patients >60 years old with New York Heart Association (NYHA) Class II or III HFrEF found significant improvements in a 6-minute walking test and a measure of quality of life.[36] In addition, the patients undergoing cardiac rehabilitation had fewer hospitalizations and spent fewer days in the hospital.[36] In light of the recent decision by the Centers for Medicare & Medicaid Services to include HFrEF as an eligible diagnosis, more effort should be made to use cardiac rehabilitation for appropriate patients.[37]

Exercise training alone may improve the quality of life for patients with HF, but has not been shown to improve mortality.[38] A large trial evaluated 2,331 stable outpatients with HFrEF (median EF 25%) who were randomized to 36 sessions (over 3 months) of supervised exercise training or usual care.[39] After 30 months of follow up, the exercise group had improved HF symptoms and extended exercise duration. An 11% improvement in the combined endpoint of death or HF hospitalization was seen after controlling for important clinical conditions.[39]

Exercise training has been less well studied in those with HFpEF, but does appear to be safe and modestly effective. A small randomized trial of older women with HFpEF found that a 12 week home-based exercise program improved their 6 minute walk test by about 300 feet, and significantly increased their quality of life, with no adverse events.[40] A 2021 trial randomized 349 older patients hospitalized for HF to a physical rehabilitation intervention targeting strength, balance, mobility, and endurance vs. usual care.[41] Mean scores on the Short Physical Performance Battery at 3 months were 8.3 in the intervention group vs. 6.9 in the control group (P<0.001). No significant differences in rates of rehospitalization for any cause or death from any cause were observed between the groups at 6 months.

Weight monitoring

Patients with HF should weigh themselves daily on the same scale at the same time of day, ideally first thing in the morning, with instructions to contact their clinician or use extra diuretic if weight exceeds a given level. Daily weights can often be used in concert with a telemonitoring program, to adjust the patient's regimen based on their weight.

Vaccines

COVID-19, influenza (annually) and pneumococcal (when indicated) vaccines are important for all patients with HF.

Smoking and alcohol

Smoking cessation counseling and medical therapy should be offered to all patients with HF who are currently smoking. Medical therapy consists of nicotine replacement (in any form, e.g., patch, gum, inhaler) and either bupropion or varenicline. Bupropion is safe and effective in patients with heart disease.[42] Based on current data, varenicline is likely safe in the post-MI setting, but caution is still advised in patients at highest risk with active cardiovascular disease.[43] All patients with HF should refrain from excessive alcohol intake (>1-2 drinks a day).[14] Those with alcoholic cardiomyopathy should refrain completely.

BOTTOM LINE: Managing HF is complicated, and patients need ongoing education and support for adhering to medications and making lifestyle changes. CPAP may improve symptoms among patients with obstructive sleep apnea, but adaptive servo-ventilation may worsen outcomes in central sleep apnea. Exercise training, even if very mild, and cardiac rehabilitation programs can improve quality of life and survival. Patients should monitor their weight closely, get recommended vaccinations, quit smoking, and limit or avoid alcohol.

Pharmacological management of HFrEF

While some pharmacologic therapies for HFrEF only reduce symptoms (e.g., diuretics), others can reduce hospitalizations and death: ACE inhibitors, ARBs, ARNI (i.e., sacubitril/valsartan), beta blockers, aldosterone antagonists, and SGLT-2 inhibitors. Many of the effective pharmacologic therapies used in HF work by inhibiting some component of the sympathetic nervous system (e.g., beta blockers) or the renin-angiotensin-aldosterone system (e.g., ACE inhibitors or aldosterone antagonists). Other agents, such as diuretics, work by increasing sodium and water loss through the kidneys (i.e., natriuresis/diuresis). When used correctly, these agents can effectively reduce the morbidity and mortality associated with HF.

This section reviews key pharmacological therapies that should be used in patients with HFrEF:

- diuretics
- ACE inhibitors
- ARBs
- angiotensin receptor-neprilysin inhibitors (ARNIs, i.e., sacubitril/valsartan)

- beta blockers
- aldosterone antagonists (also called mineralocorticoid receptor antagonists)
- SGLT-2 inhibitors

Since approximately 80% of HF patients are age 65 or older, clinicians must be mindful of the many ways that geriatric conditions can impact the use of medications and the potential complications arising from complex polypharmacy. Elderly patients are more likely to have contraindications to HF medications and are more susceptible to side effects. The general principles of geriatric prescribing apply: start low, go slow; titrate up as possible; increase the frequency of lab and vital sign monitoring.

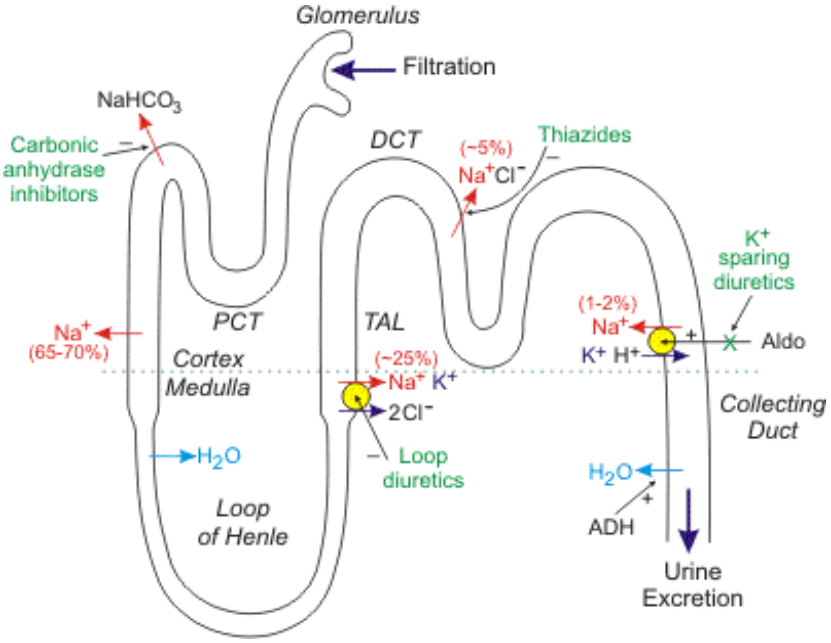
Some therapies should be specifically avoided in patients with HF:

- calcium channel blockers (non-dihydropyridine)
- NSAIDs
- many anti-arrhythmics
- thiazolidinediones (glitazones)

Diuretics

The goal of using diuretics in patients with heart failure is to achieve euvolemia and reduce symptoms of congestion, such as shortness of breath or peripheral edema. A patient's "dry weight" is generally the lowest measured weight of the patient, performed first thing in the morning, on a day when their clinician feels their volume status is normal: this should be the daily target weight. Patients should be encouraged to check their weight daily, and manage their diuretics based on this.[44] This plan can be determined in advance (e.g., "If you gain more than 1 pound in a day, take an extra dose of x mg of furosemide"). The plan may involve a telemedicine component, discussed further below. Diuretics should be combined with salt restriction, and in some cases fluid restriction, for maximal efficacy.[16]

Figure 9: Diuretic types and site of effects on nephron



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Diuretics are primarily used to treat clinical signs and symptoms of volume overload. A meta-analysis of randomized placebo-controlled trials of diuretics (primarily loop or thiazide diuretics) found that these drugs reduce the risk of death in patients with HF, although sample sizes were small and confidence intervals wide.[45] Diuretics also improved exercise capacity, and reduced the risk of worsening HF (odds ratio 0.31; 95% CI: 0.15–0.62, p=0.001).[45]

Loop diuretics

Loop diuretics are preferred for volume management in patients with HF.[46] These agents induce greater sodium excretion than any other diuretic type (they inhibit up to 25% of sodium reabsorption). Furosemide is most commonly-used, based on its low cost and effectiveness in most patients. Torsemide and bumetanide have better and more predictable oral absorption than furosemide, and can be used in patients with poor oral absorption of medications, which is a particular concern for patients with right-sided heart failure and bowel edema. Dosing of loop diuretics generally needs to be higher with impaired renal function. Ethacrynic acid is a loop diuretic but not a sulfonamide, so it can be used in patients with sulfa allergy, although it is rarely used otherwise due to higher risk of ototoxicity. Starting dose of furosemide in treatment-naïve patients is typically 20-40mg daily. Non-responders should be treated with increasing doses rather than increasing frequency of medication.

Thiazides

Thiazides are less effective than loop diuretics because they inhibit only 3%-5% of sodium reabsorption.[46] but when used together the combination can cause potent diuresis. If patients continue to have hypervolemia despite adequate doses of loop diuretics, a thiazide can be added temporarily, or on an as-needed basis (based on weight or symptoms). Chronic daily use of thiazides combined with a loop diuretic is discouraged, given the risk of electrolyte disturbances and volume depletion, and these patients should be very closely followed. Chlorothiazide or metolazone are the most commonly used in HF.

Dosing

The goal of diuretic therapy is to improve HF symptoms and eliminate volume retention. Diuretic dose must be adjusted to maintain fluid balance because an inadequate dose will allow fluid retention and diminished response to other HF medications while an overly high dose will cause hypotension, volume depletion, and an increased risk of renal insufficiency.[1] Diuretic dose should be started low and titrated upwards until the patient's "dry" weight is achieved. The dose may need to be adjusted with concomitant use of an ARNI or SGLT-2 inhibitor.

Table 7: Initial and maximum daily doses for common diuretics[1]

Drug	Initial daily dose	Maximum label total daily dose
Loop		
Bumetanide (Bumex)	0.5-1 mg daily or BID	10 mg
Furosemide (Lasix)	20-40 mg daily or BID	600 mg
Torsemide (Demadex)	10-20 mg daily	200 mg
Thiazide		
Chlorothiazide (Diuril)	250-500 mg daily or BID	1000 mg
Hydrochlorothiazide (Microzide)	25 mg daily or BID	200 mg
Metolazone (Zaroxolyn)	2.5 mg daily	20 mg

Safety

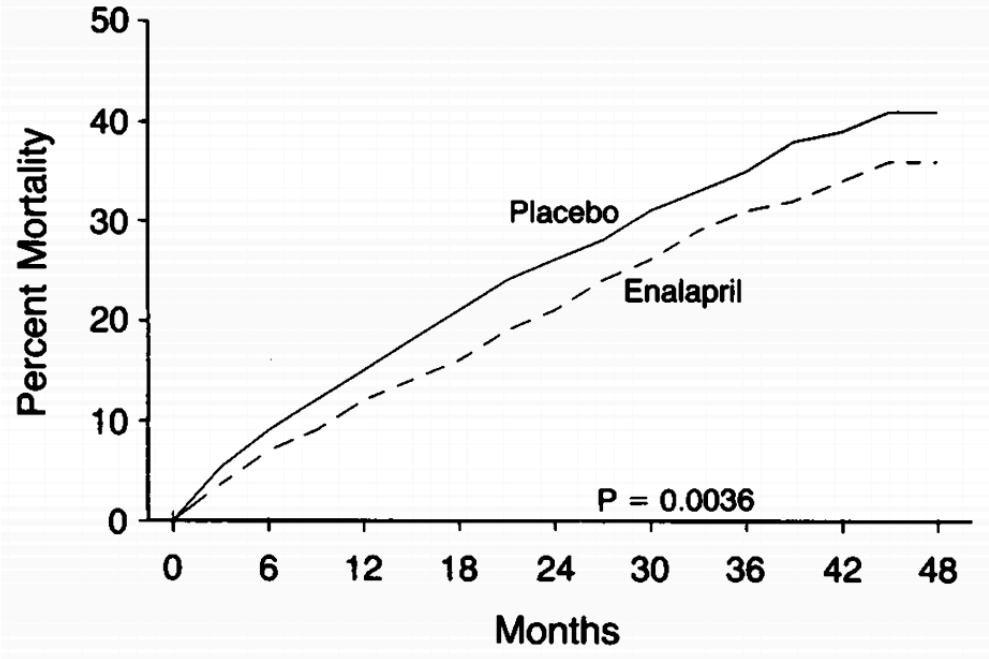
All diuretics can cause electrolyte and metabolic disturbances (e.g., hypokalemia, hyperuricemia), which are generally dose-dependent.

BOTTOM LINE: Diuretics are primarily used to improve symptoms and volume status in patients with HF. Loop diuretics, such as furosemide, are first-line therapy; torsemide and bumetanide may have better oral absorption than furosemide, and ethacrynic acid can be used for sulfonamide allergic patients. This class can be combined with thiazides to enhance diuresis, but serum electrolytes should be followed closely. Patients should be monitored for adverse effects of diuretics, primarily electrolyte derangements and renal dysfunction.

ACE inhibitors

ACE inhibitors reduce mortality in patients with symptomatic HFrEF. In the landmark **CONSENSUS trial**, patients with NYHA class IV HF randomized to enalapril (2.5mg to 40mg daily) had significantly lower 6-month mortality than those randomized to placebo (26% versus 44%, 40% relative reduction, p=0.002).[47] A subsequent large randomized trial of patients with less symptomatic HF and EF <35% (SOLVD) found a significant 16% relative reduction in mortality and heart failure hospitalizations in those randomized to enalapril versus placebo (Figure 10).[48] ACE inhibitors also significantly reduce mortality, HF hospitalizations, and incidence of HF symptoms in asymptomatic patients with reduced EF (<40%).[49]

Figure 10: Percent mortality in patients with reduced EF (<35%) in enalapril versus placebo (SOLVD trial)[48]



A meta-analysis of trials evaluating four ACE inhibitors (captopril, enalapril, ramipril, and trandolapril) shows that the benefits of ACE inhibitors are a class effect.

Sub-group analyses from the **SOLVD** and **V-HeFT trials** found that the survival benefit of ACE inhibitors was seen in white HF patients and not in Black HF patients.[50] Given that this effect has only been studied in subgroup analyses, the current guidelines recommend that ACE inhibitors be used as first line treatment for HFrEF in all patients, regardless of race.

Dose and type

The goal dose of ACE inhibitor should be consistent with those used in clinical trials. In general, a low dose of an ACE inhibitor is better than no ACE inhibitor, but clinical trials demonstrated better outcomes with higher doses. The ATLAS trial, for example, compared low-dose (2.5–5 mg/d) to standard-dose (average 32.5–35 mg/d) lisinopril and found that the standard dose resulted in a non-significant 8% lower mortality, but a significant 24% reduction in hospitalization.[51] There were higher rates of dizziness and hypotension in the standard-dose group, but similar rates of discontinuation between the groups. Given this, patients should be titrated to the highest tolerable dose (without adverse effects), being mindful that any dose is beneficial. No data support the superiority of any one ACE inhibitor over another.

Table 8: ACE inhibitor dosing[1]

	Initial dose	Maximum dose	Mean doses achieved in trials
captopril	6.25 mg TID	50 mg TID	123 mg/day
enalapril	2.5 mg BID	10-20 mg BID	17 mg/day
fosinopril	5-10 mg daily	40 mg daily	
lisinopril	2.5-5 mg daily	20-40 mg daily	35 mg/day
perindopril	2 mg daily	8-16 mg daily	
quinapril	5 mg BID	20 mg BID	
ramipril	1.25-2.5 mg daily	10 mg daily	
trandolapril	1 mg daily	4 mg daily	

Safety

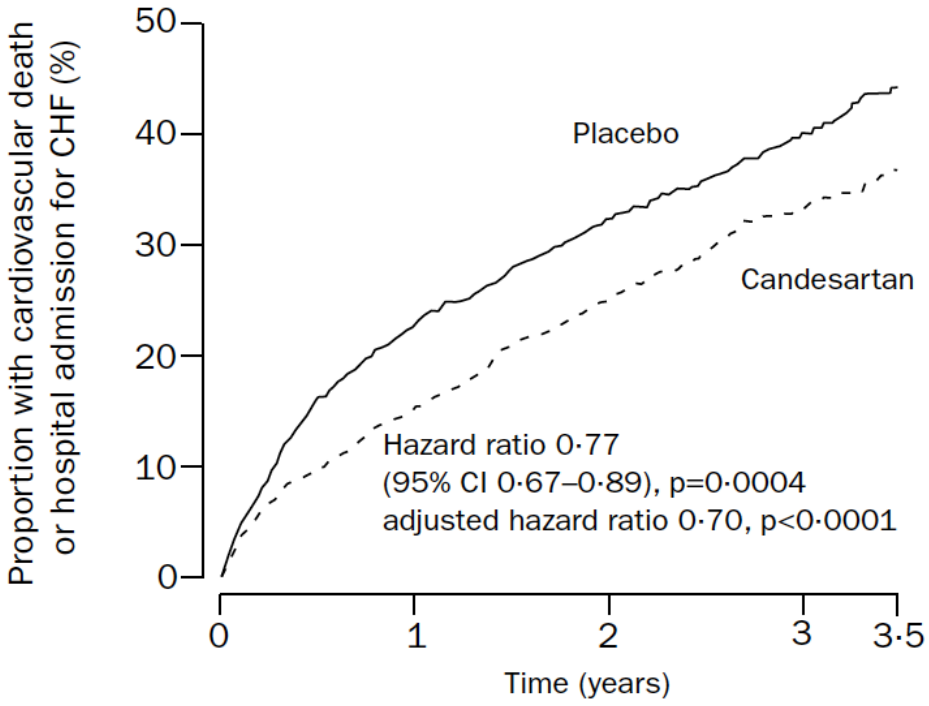
Although most HF patients (85–90%) can tolerate ACE inhibitors, some side effects (e.g., dizziness, cough) are common, and other adverse events (e.g., elevated serum potassium or creatinine levels, angioedema) are possible. If cough is a serious side effect, consider switching to an ARB.

BOTTOM LINE: ACE inhibitors reduce morbidity and mortality in patients with symptomatic HFrEF. Any dose of ACE inhibitor is beneficial; higher doses may reduce hospitalizations, but are associated with higher risks of adverse events. Titrate to the maximally tolerated dose and only use lower doses if necessary. Cough is best addressed by switching to an ARB.

Angiotensin Receptor Blockers (ARBs)

Like ACE inhibitors, ARBs have been shown to reduce mortality and hospitalizations in patients with HFrEF, although this literature is smaller than that supporting ACE inhibitors. The **CHARM Alternative trial** studied patients with HFrEF who were intolerant of ACE inhibitors. Those treated with candesartan had a 23% reduction in their risk for cardiovascular death or hospital admission for HF compared with those on placebo (Figure 11).[52]

Figure 11: Risk reduction with candesartan vs. placebo[53]



Combination therapy with an ACE inhibitor and ARB is not recommended. Combining an ARB with an ACE inhibitor was studied in the **V-HeFT trial**. Patients with HFrEF with mild-severe symptoms on optimal medical therapy (including an ACE inhibitor) were randomized to valsartan or placebo. The trial found that combination therapy (ARB and ACE inhibitor) compared to ACE inhibitor alone was associated with significant reductions in the combined outcome of morality, cardiac arrest, HF hospitalization, or IV inotrope/vasodilator for 4 hours.[54] However combination therapy had an adverse effect on mortality among patients taking an ACE inhibitor, ARB, and beta blocker. In meta-analyses, combination therapy is associated with a 37% higher risk of medication discontinuation due to adverse events.

A 2012 meta-analysis of 22 studies evaluated the effects of ARBs in 17,900 patients with EF ≤40% (mean 2.2 years).[55] Compared to ACE inhibitors, ARBs were associated with similar rates of mortality and hospitalizations. The difference in mortality and hospitalization rates between placebo and ARBs, did not reach statistical significance, however ARBs did have a trend towards improved rates. Furthermore, withdrawal due to adverse effects were 37% lower with ARBs compared to ACE inhibitors (RR 0.63; 95% CI: 0.52-0.76). Because large randomized, placebo-controlled trials, such as **CHARM Alternative**,[53] demonstrated a positive clinical effect of ARBs in patients unable to tolerate ACE inhibitors, ARBs are considered alternative first-line therapy to ACE inhibitors in patients with HFrEF.

Dose and type

As with ACE inhibitors, the goal of ARB dosing should be to titrate up to a maximally tolerated dose. Higher doses of ARBs have greater clinical impact but are associated with more adverse events, such as renal insufficiency or hyperkalemia. Thus patients undergoing dose titration must be monitored closely.

Clinical benefit is still seen even if the maximally tolerated dose is lower than doses studied in clinical trials.[56]

Table 9: Dosing for ARBs[1]

	Initial dose	Maximum dose	Mean doses achieved in trials
candesartan	4-8 mg daily	32 mg daily	24 mg/day
losartan	25-50 mg daily	50-150 mg daily	129 mg/day
valsartan	20-40 mg BID	160 mg BID	254 mg/day

Safety

Side effects of ARBs are similar to ACE inhibitors except that ARBs pose a lower risk of cough and angioedema and a *higher* rate of hypotension. In the CHARM-overall trial, ARBs were significantly more likely than placebo to cause hypotension, as well as a significant increase in serum creatinine and potassium.[57] Not all patients can tolerate ACE inhibitors or ARBs: both classes should be avoided in patients with severe renal artery stenosis, systolic BP <80 mm Hg; serum creatinine >3 mg/dL; and serum potassium >5 mEq/L.

BOTTOM LINE: In patients with HFrEF, ARBs reduce morbidity and mortality. Higher doses of ARBs have greater clinical impact but are associated with more adverse events, so doses should be titrated carefully. ACE inhibitors and ARBs should not be routinely combined due to the increased risk of adverse effects.

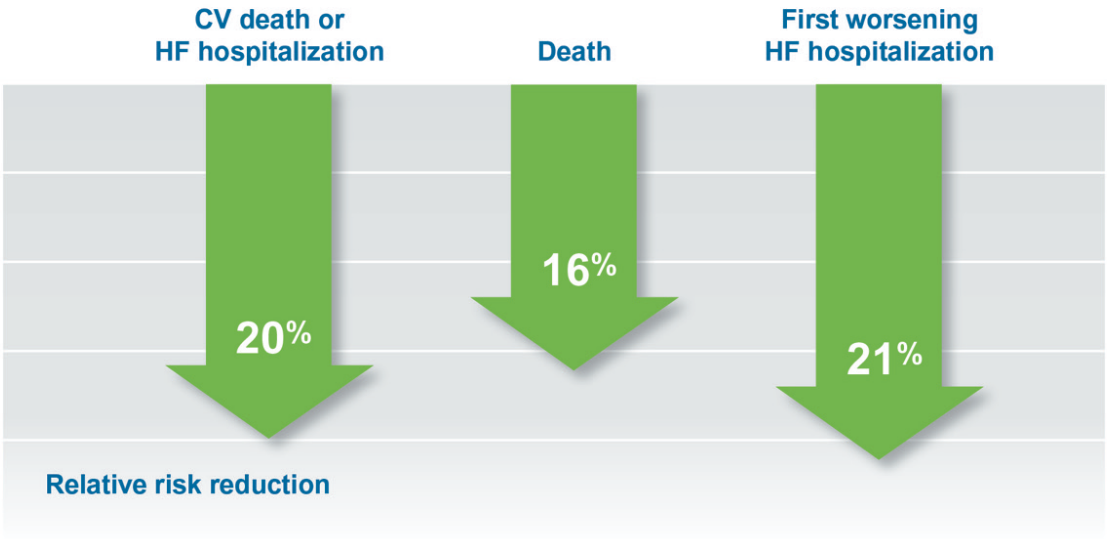
Angiotensin receptor-neprilysin inhibitors

Neprilisyn is an endogenous chemical that breaks down beneficial endogenous vasoactive peptides, including natriuretic peptides. Sacubitril inhibits neprilisyn and counteracts the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling.[58] It also promotes diuresis and natriuresis.[58] Since inhibiting neprilisyn may increase the production of angiotensin converting enzyme, however, the drug is combined with the ARB valsartan (i.e., ARNI), to simultaneously inhibit the renin-angiotensin system.

The combination of sacubitril and valsartan (Entresto) was studied in the **PARADIGM-HF trial**.[59] In this randomized controlled trial (RCT), 8399 patients with chronic HF and reduced EF (<35-40%), elevated BNP, and mild to severe HF symptoms on optimal medical therapy were randomized to sacubitril/valsartan 200 mg twice daily or enalapril 10 mg twice daily. Prior to randomization, patients underwent a 6-8 week run-in period where they sequentially received maximum dose enalapril and maximum dose sacubitril/valsartan. Patients tolerating both medications were randomized in the study; about 20% of patients did not tolerate both medications and were not included in the analysis. The majority of patients in the study were on a beta blocker and diuretic and about half were taking an aldosterone receptor antagonist.

Compared to enalapril, sacubitril/valsartan reduced the combined end-point of CV death and HF hospitalization by 20% (HR 0.8; 95% CI: 0.73-0.87, p <0.001). Additionally, sacubitril/valsartan reduced the relative risk of all-cause mortality by 16% (p < 0.001).

Figure 12: In PARADIGM-HF, sacubitril/valsartan improved patient outcomes more than enalapril alone[59]



The side effects of sacubitril/valsartan were similar to enalapril, although the incidence of symptomatic hypotension was higher with sacubitril/valsartan (14% vs. 9%, p<0.001). Patients in the sacubitril/valsartan arm had less severe hyperkalemia than control (4.3% vs. 5.6%, p=0.01), less renal dysfunction (3.3% vs. 4.5%) and similar rates of angioedema (0.2% vs. 0.1%, p=0.19).[59]

The **PIONEER-HF trial** randomized 881 patients hospitalized with acute decompensated HF (29% *de novo* HF) to sacubitril/valsartan vs. enalapril.[60] The combination therapy reduced rates of an exploratory composite endpoint (all-cause death, rehospitalization for HF, LVAD implantation, or heart transplant listing, HR 0.54; 95% CI: 0.37-0.79.) A reduction in HF hospitalization was observed within 30 days of randomization and patients in the two study arms experienced similar rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema.

Dosing and safety

Given the evidence for a survival benefit, patients should be treated with sacubitril/valsartan rather than an ACE inhibitor or an ARB, although the combination medication can be costly or may not be tolerated by every patient.[25] Specific steps should be followed for initiation, dosing, and monitoring for combination therapy:[25]

- initiation
  - if previously on ACE inhibitor: stop the ACE inhibitor and start ARNI after 36 hour wash out to reduce risk of angioedema
  - if previously on ARB: can start directly
- initial dose:
  - 49/51 mg BID if on equivalent of >10 mg enalapril or >160 mg valsartan
  - 24/26 mg BID if on lower doses of ACE inhibitor/ARB, ACE inhibitor/ARB naïve, elderly, renal dysfunction, moderate hepatic impairment (Child-Pugh class B)

  - titrate to target dose of 97/103 mg bid if possible
- monitoring:
  - blood pressure
  - electrolytes and renal function (1-2 weeks after initiation or dose increase)

BOTTOM LINE: Sacubitril/valsartan should be used to reduce mortality and HF hospitalizations and should replace an ACE inhibitor or ARB in patients who are able to both tolerate and afford it. Patients transitioning from an ACE inhibitor to sacubitril/valsartan require a 36-hour washout of the ACE inhibitor before starting sacubitril/valsartan.

Beta blockers

Beta blockers can target various adrenergic receptors:

- β_1-receptor blockade: slows heart rate
- β_2-receptor blockade: causes smooth muscle contraction, including bronchospasm
- α-receptor blockade: causes peripheral vasodilation

Bisoprolol and metoprolol are β_1-selective, while carvedilol has activity at β_1, β_2, and α receptors. One of these three beta blockers should be used in all patients with HFrEF who are already on an ACE inhibitor and still symptomatic. This is based on the randomized controlled trials summarized in Table 10.

Table 10: Key studies of beta blockers in heart failure[61,62]

	CIBIS-II	MERIT-HF	Carvedilol trial
Beta blocker studied	bisprolol	metoprolol XL	carvedilol
Mean age	61 years	64 years	63 years
LVEF	≤35%	≤40%	≤25%
NYHA Class	III-IV	II-IV	III-IV
Patients on ACE inhibitor or ARB	96%	90%	97%
Patients on diuretics	99%	90%	99%
Length of follow-up (mean)	1.3 years	1 year	10.4 months

Dose and type

If a beta-blocker is started, it should be titrated to the highest tolerated dose. One randomized trial found a benefit of higher versus lower dosing of carvedilol on left ventricular function and mortality at six months in patients with HFrEF.[63] Beta blockers differ in their pharmacological profiles and, therefore, a class effect cannot be assumed and only the three beta blockers that have been studied in heart failure should be used.

Carvedilol was compared to short-acting metoprolol (metoprolol tartrate) in the **COMET tri**al, which enrolled heart failure patients with HFrEF.[64] Patients taking carvedilol had a 17% lower risk of death

compared to patients taking metoprolol tartrate (HR 0.83; 95% CI: 0.74-0.93, p=0.0017). Therefore short-acting metoprolol tartrate is not recommended for the long-term treatment of patients with heart failure. One concern with this study was the lower dosing of metoprolol tartrate; some authors have speculated that improved results might have been seen with more frequent dosing.

Table 11: Mortality after treatment with carvedilol in HFrEF.[63]

Treatment	Mortality (at 6 months)
Placebo	16%
Low-medium dose carvedilol (6.25 mg-12.5 mg BID)	6-7%
High dose carvedilol (25 mg BID)	1%

Indirect evidence suggests that carvedilol (which has vasodilating effects) may be superior to non-vasodilating beta blockers (e.g., bisoprolol or metoprolol). A meta-analysis of 21 trials in almost 6,000 HF patients (with both reduced and preserved EF) found that overall mortality reduction was greater with carvedilol than the other beta blockers (54% versus 27%, p=0.007), particularly in patients without ischemic heart disease.[65] Carvedilol lowers blood pressure more than the other agents, and may be the best agent in patients who also have hypertension.

Table 12: Beta blocker dosing[1]

	Initial daily dose	Maximum dose	Mean dose achieved in trials
bisoprolol	1.25 mg daily	10 mg daily	8.6 mg/d
carvedilol	3.125 mg BID	50 mg BID	37 mg/d
carvedilol CR	10 mg daily	80 mg daily	
metoprolol XL	12.5-25 mg daily	200 mg daily	159 mg/d

Safety

In HF clinical trials, beta blockers were very well tolerated, with discontinuation rates lower than those for placebo.[61,66]

Side effects of beta blockers include:[1]

- fluid retention and worsening HF (may improve with intensification of other therapies e.g., diuretics)
- fatigue, sexual dysfunction
- bradycardia or heart block
- hypotension (reduce diuretic therapy as appropriate; stagger dosing with ACE inhibitor)

Absolute contraindications for beta blockers include:[1]

- third degree heart block
- history of severe bronchospasm

Relative contraindications include:[1]

- bradycardia <60 bpm
- symptomatic hypotension
- severe peripheral arterial disease

Patients with mild-to-moderate bronchospasm usually tolerate β_1-selective beta blockers (i.e., metoprolol, bisoprolol), which have shown a survival benefit

BOTTOM LINE: Beta-blockers should be used in all patients with HFrEF who have current or prior HF symptoms. The dose of an angiotensin system blocker (i.e., ACE inhibitor, ARB, ARNI) does not need to be maximized before starting a beta blocker. Guidelines recommend carvedilol, metoprolol XL (extended release), or bisoprolol. Short-acting metoprolol is not recommended.

Dose should be titrated to the lowest tolerated heart rate. Continue with a beta blocker even if symptoms do not improve, unless intolerance or significant side effects are present, in which case taper to discontinuation.

Aldosterone-receptor antagonists

Two aldosterone receptor antagonists are currently approved in the United States for the treatment of patients with HFrEF: spironolactone and eplerenone. Although both medications block activity at the aldosterone receptor, eplerenone is more selective. While numerous clinical trials have evaluated the efficacy of each drug, no studies have directly compared spironolactone and eplerenone. Both have been shown to improve morbidity and mortality in patients with HFrEF, although both also increase the risk of hyperkalemia.

Table 13: Aldosterone antagonist study results

	RALES[67]	EPHESUS[68]	EMPHASIS-HF[69]
Drug studied	spironolactone	eplerenone	eplerenone
All-cause mortality, treatment vs. placebo	30% reduction (p<0.001)	15% reduction (p=0.008)	22% reduction (p=0.01)
HF-related hospitalization, treatment vs. placebo	35% reduction (p<0.001)	15% reduction (p=0.03)	39% reduction (p<0.001)

Safety and dosing

The primary safety concern with aldosterone receptor antagonists is renal function decline and hyperkalemia. In the RALES trial, the median creatinine increase was 0.05–0.10 mg/dL and the median potassium increase was 0.30 mmol/L (at a mean study dose of 25 mg).[67] In this trial, serious hyperkalemia occurred in 2% of the study group and 1% of the placebo group.[67]

Similar results were found in the EMPHASIS-HF trial: potassium levels of >5.5 mmol/L were experienced by 7.2% of patients in the eplerenone group vs. 1.8% in the control group (p<0.001).[69]

A population-based study of routine care found that after the publication of the RALES trial, as the rate of spironolactone use increased from 34 to 149 per 1,000 HF patients, hospitalizations due to hyperkalemia also increased from 2 to 11 per 1,000 patients from 1994 to 2001.[70]

Spironolactone can also cause endocrine side effects, which occurred in 10% of the treatment group in RALES (versus 3% of the placebo group).[67] These included gynecomastia, breast pain, menstrual irregularities, impotence, and decreased libido. Discontinuation rates due to adverse events occurred in 8% of the treatment group and 5% of the placebo group. Gynecomastia or breast pain is less common with eplerenone.

The ACCF/AHA recommends against starting aldosterone antagonists in patients with:[1]

- creatinine >2.5 mg/dL (in men); >2.0 mg/dL (in women)
- serum potassium >5.0 mEq/L

The ACCF/AHA/HFSA recommends the following to reduce the risk of hyperkalemia and renal dysfunction associated with aldosterone antagonists:[1]

- avoid NSAIDs
- reduce or discontinue all potassium supplements
- closely monitor potassium and creatinine levels (check with basic metabolic panel within 3 days of drug initiation, then 1 week, then monthly for the first 3 months, and every three months thereafter)

Table 14: Dosing recommendations for aldosterone antagonists[1]

	Eplerenone		Spironolactone	
eGFR*	≥50	30-49	≥50	30-49
Initial dose	25 mg daily	25 mg QOD	12.5-25 mg daily	12.5 mg daily or QOD
Maintenance dose	50 mg daily	25 mg daily	25 mg daily or BID	12.5-25 mg daily
*eGFR = estimated glomerular filtration rate (mL/min/1.73m^2)				

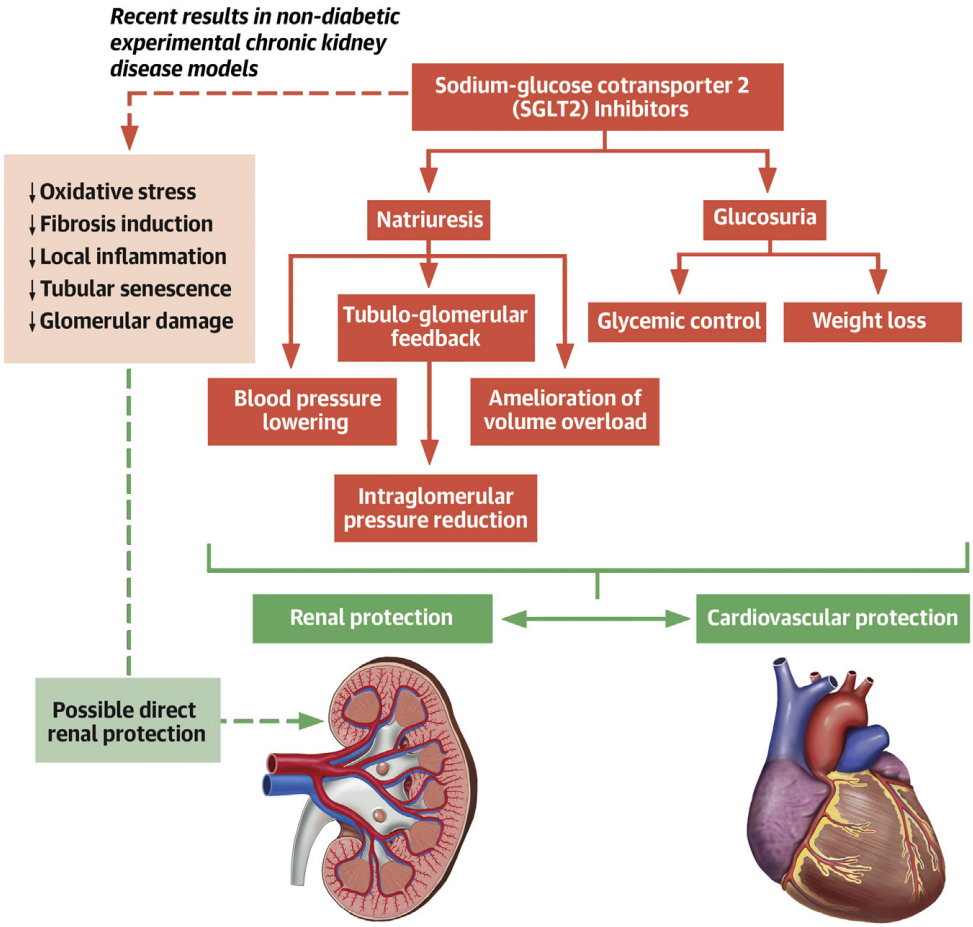
BOTTOM LINE: Aldosterone receptor antagonists can reduce mortality and morbidity in patients with HFrEF and HF symptoms. These agents can increase creatinine and potassium levels in a dose-dependent fashion and should not be used in those with creatinine >2.5 mg/dL (men) or >2.0 mg/dL (women). Angiotensin system blockers or beta blockers do not need to be optimized before starting an aldosterone antagonist. Discontinue potassium supplements and avoid high-potassium foods. Monitor potassium and renal function at 3 days and again 1 week after initiation of therapy, then monthly for the first 3 months. Risk of hyperkalemia is increased with use of high-dose ACE inhibitors.

Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors

SGLT-2 inhibitors were initially developed and approved as glucose-lowering agents, but their use has now been shown to be associated with reductions in atherosclerotic events, hospitalization for heart

failure, cardiovascular and total mortality, and progression of chronic kidney disease.[71] These agents are now being studied for treating HF even in patients without diabetes. SGLT-2 inhibitors may confer benefits via natriuresis and glucosuria, which lower cardiac pre-load and may reduce pulmonary congestion and systemic edema (Figure 13).

Figure 13: SGLT-2 inhibitor proposed mechanisms of action[71]



SGLT-2 inhibitors for patients with HF were evaluated in two randomized clinical trials, **DAPA-HF** (2019) and **EMPEROR-Reduced** (2020) (Table 15).

Table 15: Summary of key trials evaluating SGLT-2 inhibitors in HF[72,73]

	DAPA-HF	EMPEROR-Reduced
Drug studied	Dapagliflozin 10 mg	Empagliflozin 10 mg
Inclusion criteria:	Chronic HF	Chronic HF
LVEF	≤40%	≤40%
NYHA class	II-IV	II-IV
NT-proBNP (pg/mL)	≥400, if recent HF hospitalization ≥600 ≥900, if in atrial fibrillation	≥600, if LVEF ≤30% or recent HF hospitalization ≥1000, if LVEF 31-35% ≥2500, if LVEF 36-40% ≥5000, if in atrial fibrillation
Key exclusion criteria:		
Diabetes	Type 1 diabetes mellitus	History of ketoacidosis
eGFR (mL/min/1.73 m^2)	<30	<20
Others	Symptomatic hypotension, acute decompensated HF, recent MI	Symptomatic hypotension, acute decompensated HF, recent MI
Median follow-up	18 months	16 months

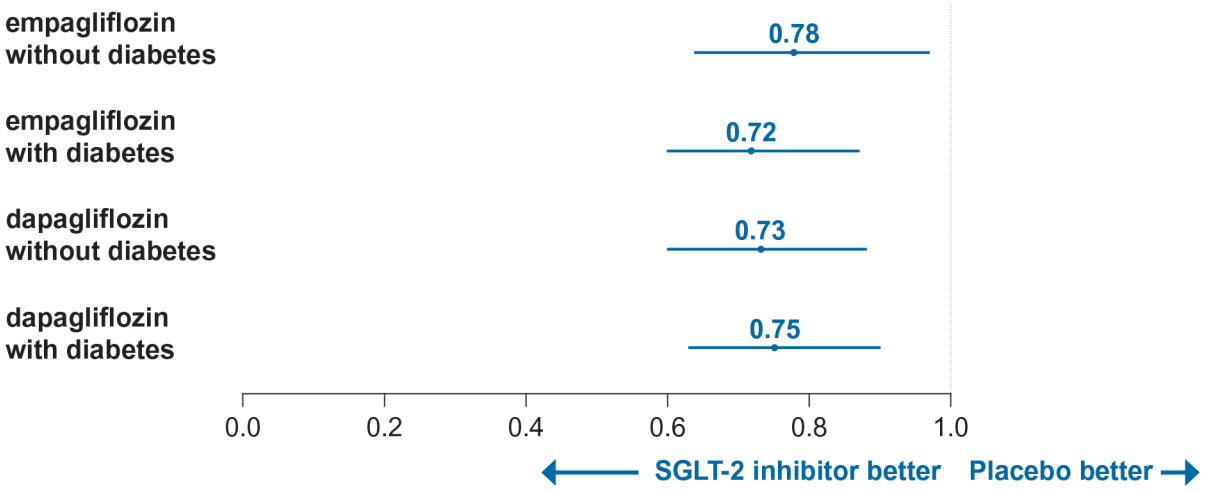
Both trials demonstrated significant reductions in a range of clinical outcomes including cardiovascular death, first hospitalization for HF, and all-cause death (Table 16).

Table 16: Clinical outcomes from DAPA-HF and EMPEROR-Reduced trials[72-74]

	DAPA-HF	EMPEROR-Reduced	Meta-analysis of both studies
CV death or first HF hospitalization	0.75 (0.65-0.85)	0.75 (0.65-0.86)	0.74 (0.65-0.86)
First HF hospitalization	0.70 (0.59-0.83)	0.69 (0.59-0.81)	0.69 (0.62-0.78)
CV death	0.82 (0.69-0.98)	0.92 (0.75-1.12)	0.86 (0.76-0.98)
All-cause mortality	0.83 (0.71-0.97)	0.92 (0.77-1.10)	0.87 (0.77-0.98)
Worsening renal function*	0.71 (0.44-1.16)	0.52 (0.29-0.92)	0.62 (0.43-0.90)
Total (first and recurrent) HF hospitalization and CV death	0.75 (0.65-0.88)	0.76 (0.65-0.89)	0.75 (0.68-0.84)

The reduction in important clinical outcomes was observed regardless of the diabetes status of patients, as can be seen in the results of a meta-analysis of a composite outcome of first heart failure hospitalization or CV death from both trials (Figure 14).

Figure 14: Meta-analysis of from DAPA-HF and EMPEROR-Reduced trials by diabetes status[74]



Safety and dosing

Safety and adverse event data from the **DAPA-HF** and **EMPEROR-Reduced** trials shows no significant differences between either of the SGLT-2 inhibitors studied and placebo (Table 17).

Table 17: Safety profiles of SGLT-2 in key HF trials[72,73]

	DAPA-HF		EMPEROR-Reduced	
Adverse events	**Dapagliflozin**	Placebo	**Empagliflozin**	**Placebo**
Volume depletion	7.5%	6.8%	10.6%	9.9%
Severe hypoglycemia	0.2%	0.2%	0.3%	0.4%
Diabetic ketoacidosis	0.1%	0	0	0
Renal adverse event	6.0%	6.7%	9.4%	10.3%
Limb amputation	0.5%	0.5%	0.7%	0.5%
Fournier's gangrene	0	<0.1%	0.1%	0

Based on existing evidence, SGLT-2 inhibitors are recommended agents in the 2021 American College of Cardiology expert consensus document, although these agents may be expensive (i.e., typical non-discounted cash price approximately $600/month).[25] The clinical use of SGLT-2 inhibitors can be summarized as:

- dosing (no titration):
  - dapagliflozin 10mg daily
  - empagliflozin 10mg daily
- contraindications:
  - type 1 diabetes or prior ketoacidosis
  - on dialysis
- caution:
  - be mindful of volume depletion--may need to adjust diuretics
  - discuss increased risk of urogenital infections with patients
  - use cautiously in patients with eGFR <20 for empagliflozin and eGFR <30 for dapagliflozin

Add-on therapies

Several agents may be helpful when patients are still symptomatic despite optimal medical management:

- hydralazine and isosorbide dinitrate (may be particularly effective in Black patients)
- ivabradine (for patients in sinus rhythm if heart rate is >70 bpm)
- digoxin

Therapies to avoid in patients with HF include:

- calcium channel blockers (non-dihydropyridine)
- NSAIDs
- many anti-arrhythmics
- thiazolidinediones (glitazones)

Hydralazine and isosorbide dinitrate

Hydralazine and isosorbide dinitrate lead to nitric oxide-mediated vasodilatation.[75] The **V-HeFT II** trial compared the combination of hydralazine and isosorbide dinitrate to enalapril in men with HFrEF and predominately mild to moderate HF symptoms.[76] Two year mortality was lower with enalapril compared to hydralazine/isosorbide dinitrate (18% versus 25%, p=0.016) although overall mortality did not reach statistical significance (p=0.08). Subgroup analysis demonstrated that the survival benefit of enalapril was experienced by White patients, whereas there was no difference between therapies in Black patients. The **A-HeFT trial** subsequently randomized 1,050 Black patients with HFrEF with moderate-severe heart failure symptoms to receive hydralazine and isosorbide dinitrate or placebo, in addition to evidence based therapies including beta blockers and ACE inhibitors or ARBs.[77] This study demonstrated a 43% reduction in death from any cause with hydralazine and isosorbide dinitrate compared to placebo (HR 0.57, p=0.01).[77] Despite this, combination therapy is not widely used in Black patients. This may be due to the inconvenience of three times a day dosing. Additionally, combination therapy leads to higher rates of hypotension and dizziness compared to placebo. Initial dosing is 25-50 mg TID for hydralazine and 20-30 mg TID for isosorbide. Titrate to maintenance doses of 100 mg TID for hydralazine and 40 mg TID for isosorbide if tolerated.

Table 18: Outcomes of hydralazine + isosorbide versus placebo in Black patients with symptomatic HF[77]

Outcome	Hydralazine + Isosorbide	Placebo	P-value
All cause mortality	6.2%	10.2%	0.02
HF hospitalization	16%	24%	0.001
Change in quality of life at 6 months (lower better)	-5.6	-2.7	0.02

BOTTOM LINE: Hydralazine combined with isosorbide dinitrate reduces mortality and HF hospitalizations in Black patients with reduced EF who are already on standard medical therapy, including beta blockers, angiotensin receptor blockers, an aldosterone receptor antagonist, and an SGLT-2 inhibitor. Combination therapy with hydralazine and isosorbide dinitrate is also recommended for patients who cannot tolerate an ACE inhibitor or ARB.

Ivabradine

Ivabradine selectively inhibits an ion channel that controls the responsiveness of the sinoatrial (SA) node, and therefore directly reduces the heart rate. This agent was evaluated in the **SHIFT trial,** which randomized recently-hospitalized patients with HFrEF on stable medical therapy with a resting heart rate >70 beats per minute to ivabradine or placebo. The majority of patients were on an ACE inhibitor/ARB and a beta-blocker, and more than half were taking an aldosterone receptor antagonist.[78]

After a median follow-up of almost 2 years, ivabradine significantly reduced the combined endpoint of CV death or HF hospitalization by 18% (95% CI: 0.75-0.9, p<0.0001).[78] This effect was driven by a reduction in HF hospitalizations (HR 0.74; 95% CI: 0.66-0.83, p<0.0001). Ivabradine did not significantly lower the risk of all-cause mortality or cardiovascular mortality and caused significantly more symptomatic bradycardia (5% vs. 1%, p<0.0001). Further analysis of the trial found the least benefit in those patients with higher beta blocker doses and lower baseline heart rates, indicating that this agent may only have a role in improving outcomes in patients who cannot tolerate or cannot reduce their heart rate with a beta blocker. Recommended dosing is 5 mg BID with an increase to 7.5 mg BID as tolerated.[79] Start with 2.5 mg BID in patients aged 75 and older or in patients with a history of conduction defects. Contraindications include:

- sick sinus syndrome or 2nd or 3rd-degree AV block without a pacemaker
- persistent AF or flutter
- atrial pacemaker dependence
- acute decompensated HF; BP <90/50 mmHg
- severe hepatic impairment (Child-Pugh C)

BOTTOM LINE: Ivabradine reduces heart rate and may help reduce HF hospitalizations, although no mortality benefit was observed in clinical trials. Recommended dosing is 5 mg BID with an increase to 7.5 mg BID as tolerated, although start with 2.5 mg BID in patients over age 75.

Digoxin

Digoxin is the most widely-used formulation of digitalis, a compound that has been used for centuries to treat cardiac conditions because of its antiarrhythmic properties. Digoxin also increases cardiac contractility, which is the primary benefit of its use in HF. The only large randomized trial of digoxin enrolled patients with an EF<45% who were already on combinations of ACE inhibitors and diuretics.[80] After about 3 years of follow-up, overall mortality and cardiac-specific mortality were no different between the groups, but significantly fewer patients in the digoxin group versus the placebo group were hospitalized for worsening heart failure (27% versus 35%, p<0.001).[80] This reduction was most pronounced in the sub-group of patients with EF<35%, enlarged ventricular size, or moderate to severe symptoms.[80] Current guidelines recommend considering the use of digoxin in patients with HFrEF, unless it is contraindicated, to decrease HF hospitalizations.[1] Digoxin therapy is typically started at a dose of 0.125 mg to 0.25 mg daily.[1]

Safety

In the digitalis trial, suspected digoxin toxicity (based on clinician suspicion) occurred in 12% of the digoxin group and 8% of the placebo group (p<0.001), although only 2% of patients had digoxin levels exceeding 2 ng/mL, indicating that symptoms of toxicity are non-specific and difficult to attribute to

increased drug levels.[48] Digoxin toxicity occurs more commonly in patients with advanced age, female sex, low BMI, and renal insufficiency. Hypokalemia, hypomagnesemia, and hypothyroidism may induce toxicity at lower serum levels. Symptoms of digoxin toxicity include:

- cardiac arrhythmias (re-entrant rhythms and heart block)
- GI symptoms (anorexia, nausea, vomiting)
- neurologic symptoms (visual disturbances, confusion)

Observational studies have suggested that patients treated with digoxin for atrial fibrillation have higher mortality than those not treated with digoxin.[80] Subsequent work, however, demonstrated that this increased risk is likely due to uncontrolled confounding, because patients treated with digoxin in observational studies tend to be sicker than those patients not treated with digoxin.[81] Digoxin has not been shown to increase mortality in randomized controlled trials in patients with heart failure and can be used to reduce hospitalizations among symptomatic patients on optimal medical therapy, as long as levels are monitored.

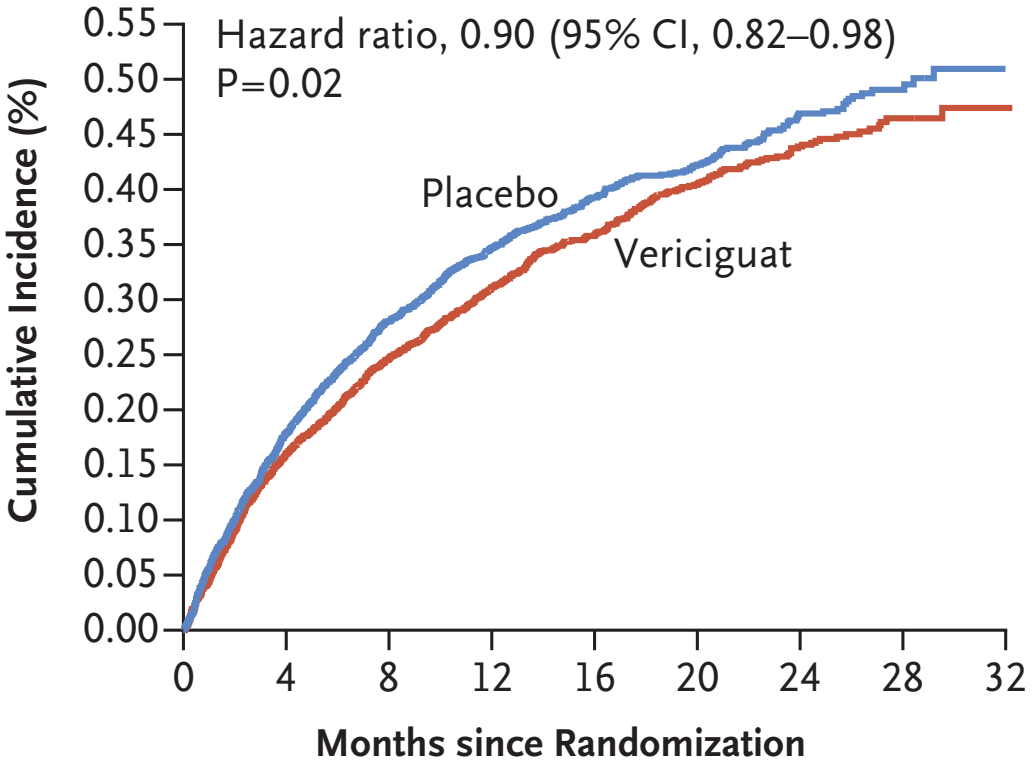
BOTTOM LINE: Digoxin is an add-on therapy for patients on optimal medical therapy but who are still symptomatic. Digoxin toxicity occurs more commonly in the elderly or those with low BMI or renal insufficiency. Digoxin therapy is typically started at a dose of 0.125 to 0.25 mg daily.

Novel therapies

Soluble guanylate cyclase stimulation

Vericiguat is a novel oral soluble guanylate cyclase stimulator that enhances the nitric oxide/cyclic guanosine monophosphate (GMP) pathway. The Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (**VICTORIA**) trial evaluated the efficacy and safety of vericiguat in 5,050 patients with HFrEF or patients with chronic heart failure and recent decompensated heart failure with a median follow-up of 10.8 months (Figure 15).[82] Patients in the vericiguat group had a 10% lower incidence of the composite endpoint of cardiovascular death or HF hospitalization, although the confidence interval includes results that may not be clinically important (HR 0.90; 95% CI: 0.82-0.98). There were no significant differences between groups on individually-analyzed endpoints of cardiovascular death, hospitalization for HF, or all-cause death.

Figure 15: Primary outcome (CV death or HF hospitalization) results from VICTORIA trial of vericiguat[82]



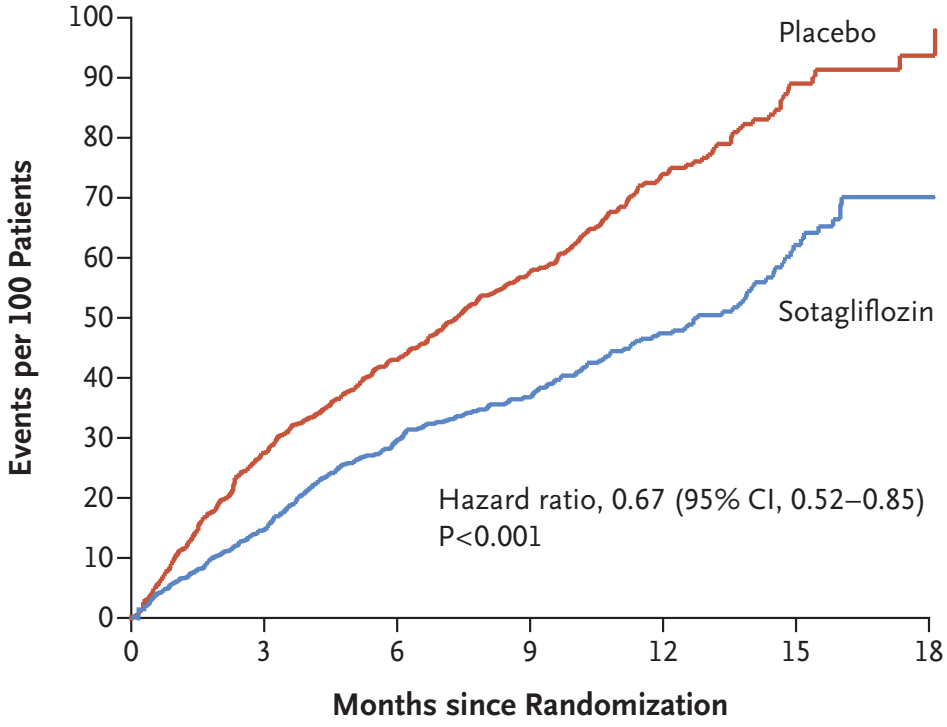
Vericiguat is FDA-approved for patients with chronic HF (LVEF ≤45%) following HF hospitalization or for outpatients using IV diuretic, although this agent has not yet been incorporated into clinical guidelines.

Sotagliflozin

Although not approved for the treatment of HF as of June, 2021, the dual inhibitor sotagliflozin has shown promise for reducing hospitalizations related to HF. Sotagliflozin is an SGLT-2 inhibitor that also inhibits some gastrointestinal SGLT-1 receptors.[83] The SGLT-2 inhibition increases urinary glucose excretion and the SGLT-1 inhibition reduces glucose levels after eating by delaying intestinal glucose absorption.

Sotagliflozin was evaluated in the **SOLOIST-WHF trial**, which randomized 1,222 patients with HF and type 2 diabetes to sotagliflozin vs. placebo for a median follow-up of 9 months (trial was stopped prematurely due to loss of funding). The primary endpoint was a composite of cardiovascular deaths and hospitalizations/urgent visits for HF. Patients in the sotagliflozin group had a 33% lower risk of the primary endpoint (HR 0.67; 95% CI: 0.52-0.85) (Figure 16) but no significant reduction was observed in cardiovascular deaths alone (HR 0.84; 95% CI: 0.58-1.22).

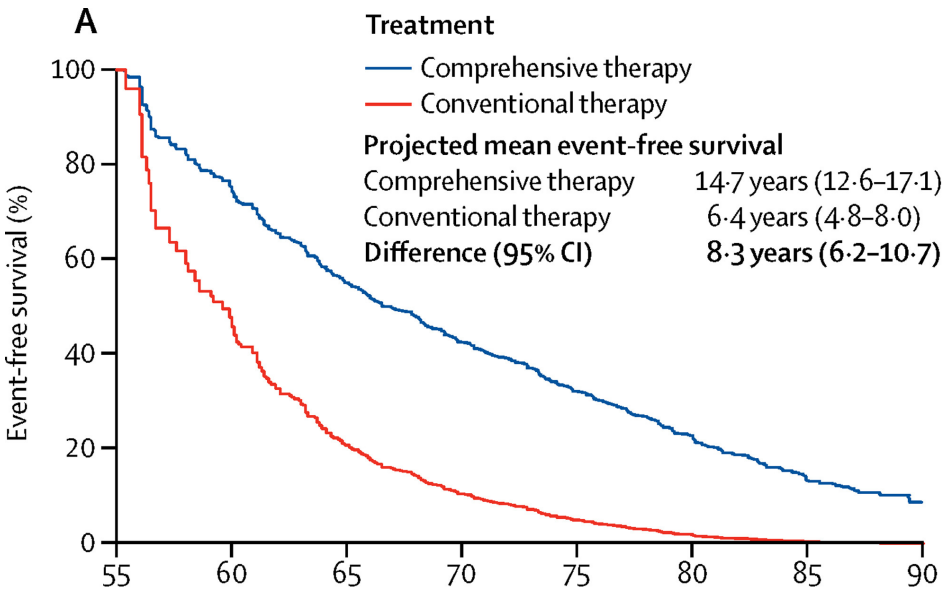
Figure 16: Results on primary endpoint in SOLOIST-WHF trial of sotagliflozin[84]



Summary of pharmacological treatments

All patients with HF, regardless of EF, should be treated for risk factors that can exacerbate their disease (e.g., hypertension, diabetes, and atrial fibrillation). Treating patients with a combination of medications has been shown to have additive benefits compared to limited conventional therapy of an ACE-inhibitor/ARB plus a beta blocker (Figure 17).

Figure 17: Benefits of comprehensive therapy with ARNI, beta blocker, aldosterone antagonists, and SGLT-2 inhibitor[85]

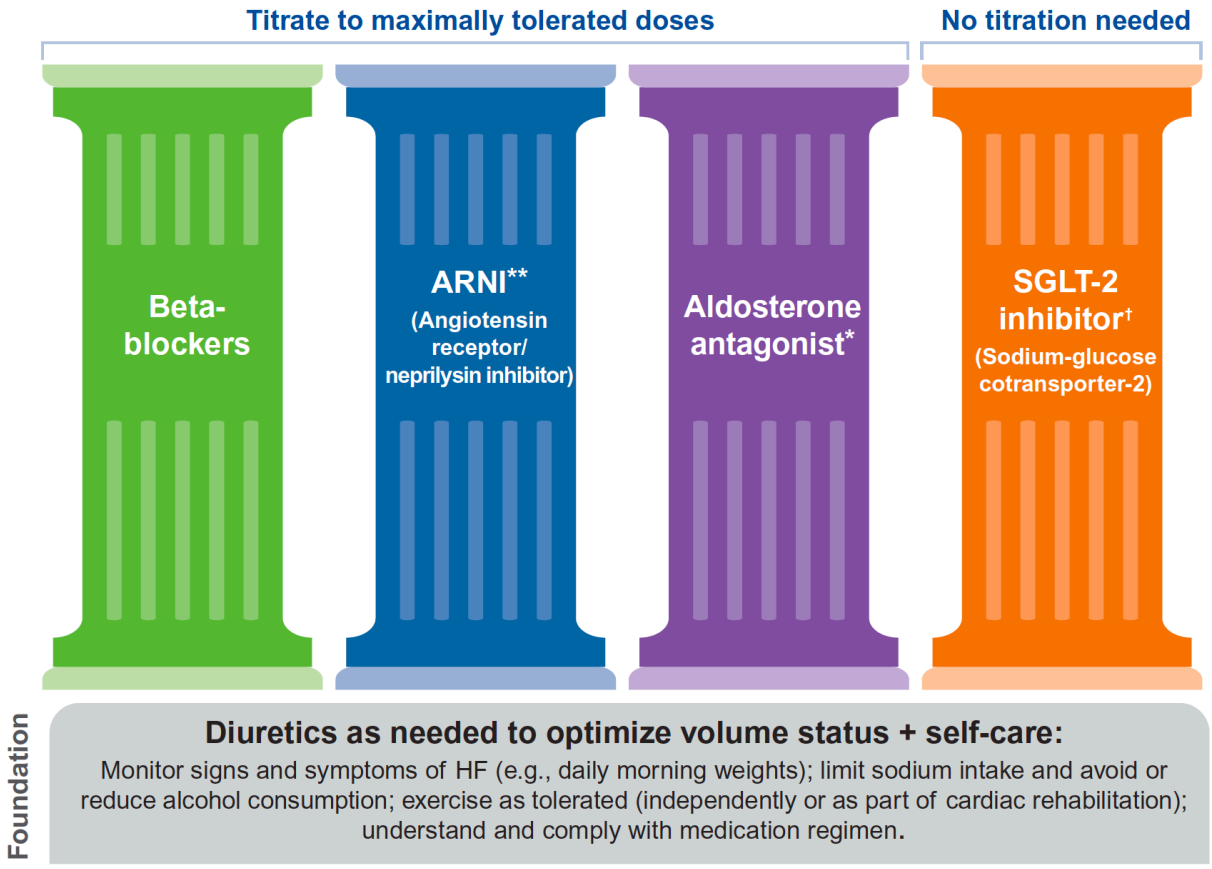


Comprehensive therapy – ARNI, SGLT-2 inhibitor, and aldosterone antagonist

Conventional therapy – ACE inhibitor or ARB plus a beta blocker

Consistent with those data, current ACC/AHA/HFSA guidelines for HFrEF combined medication regimens are summarized in Figure 18.[25]

Figure 18: Foundations of guideline-directed medical therapy for patients with HFrEF[86]



*Also known as mineralocorticoid receptor antagonist (MRA). **Can use ACE inhibitor or ARB if unable to afford or tolerate ARNI. †Dapagliflozin and empagliflozin were studied at 10 mg daily.

Tips for achieving optimal benefits from medical therapy:[25]

- titrate ARNI (ACE inhibitor or ARB if ARNI not tolerated or cost prohibitive) and beta blockers to maximally tolerated dose to achieve the greatest mortality benefit.[51,63] Even a low dose of these drugs is better than no dose.
- use a beta-blocker with benefit in heart failure (e.g., bisoprolol, carvedilol, metoprolol XL)
- SGLT-2 inhibitors do not require dose titration for heart failure. Both dapagliflozin and empagliflozin were studied at 10 mg daily.
- additional therapies for heart failure may reduce hospitalization:
  - hydralazine plus isosorbide (Bidil, generics) for Black patients
  - ivabradine (Corlanor) for patients on maximally tolerated beta-blockers with heart rate >70
  - vericiguat for patients on outpatient IV diuretics or after HF hospitalization
  - digoxin

Managing medications in older adults

Approximately 80% of HF patients are age 65 and older, hence medications must be administered with awareness of how they might affect cognition, frailty, risk of falling, urinary incontinence, and other age-

associated conditions. Elderly patients are more likely to have contraindications for HF medications and are more susceptible to side effects. Treatment strategies include the “start low/go slow” approach to dosing and titration, and increasing the frequency of follow-up, lab monitoring, and assessment of vital signs.

Devices to treat HFrEF

Patients with HFrEF are at increased risk for ventricular tachyarrhythmias, such as ventricular tachycardia or ventricular fibrillation, and sudden cardiac death (SCD), which is defined as unexpected death within one hour of onset of new cardiac symptoms.[87] SCD, in fact, accounts for 30-50% of all HF-related cardiac deaths.[88] Treatments are aimed at primary prevention (i.e., to prevent a first episode of life-threatening arrhythmia or SCD) or secondary prevention (i.e., avoidance of recurrent arrhythmia or SCD). Therapies effective for primary prevention of SCD include:

- guideline-directed medical therapies
  - beta blockers
  - ARNI/ACE inhibitors/ARB
  - aldosterone receptor antagonists
- implantable cardioverter defibrillators (ICDs)

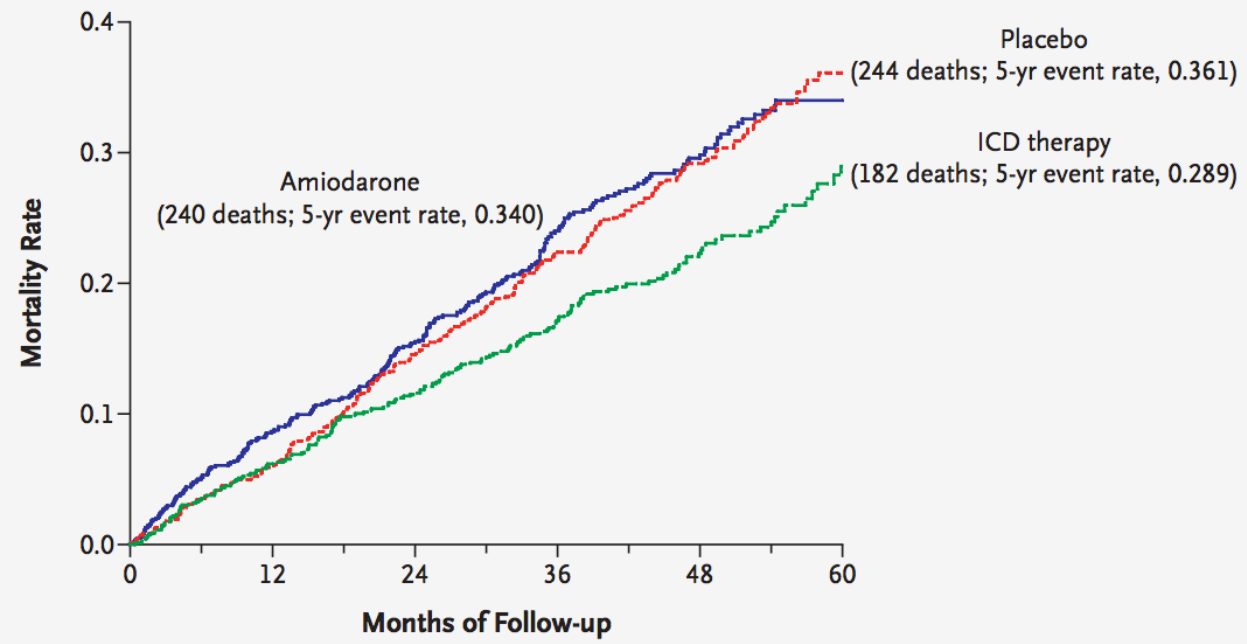
Anti-arrhythmic therapy (e.g., amiodarone) is not effective for preventing SCD in HF patients without a history of SCD.[89]

Implantable cardioverter defibrillators

ICDs use electrical shocks to terminate detected ventricular arrhythmias and help prevent SCD. ICDs can be implanted transvenously or subcutaneously.[90] Transvenous ICDs can act as both pacemakers and defibrillators. These devices have been shown to reduce mortality and, when combined with cardiac resynchronization therapy, can improve quality of life and reduce HF hospitalizations.[91,92,93] ICDs can be used as both primary prevention and secondary prevention.

ICDs reduce mortality among post-MI patients with reduced EF and patients with non-ischemic HF. Figure 19 shows the results of a trial comparing conventional therapy, an ICD, or the antiarrhythmic agent amiodarone.[89]

Figure 19: Mortality in patients with HFrEF randomized to conventional therapy, amiodarone, or ICD[89]



A meta-analysis of three large trials suggests that the benefits of ICDs may be attenuated in the elderly.[94] The average age in ICD trials is 60-64, although almost half of new ICD implants are in patients older than 70.[95]

The risks associated with ICD implantation are not trivial: about 30% of patients receiving an ICD experience at least one complication following implantation, and in 10% of these patients the complication is directly related to the procedure.[96] In a 2018 study of 20,580 device procedures with mean follow-up of 2.3 years, the rate of mechanical complications was 5.3% and the rate of infectious complications was 1.9%.[97] A meta-analysis of 18 randomized controlled trials involving ICDs found a total pooled complication rate of 9.1% (excluding inappropriate shocks) with complications including displacement, pneumothorax, hematoma, and infection.[98] The risks of complications are lower if the ICD is implanted by an experienced electrophysiologist.[96] Frequent or inappropriate shocks can lead to decreased quality of life and, in some cases, post-traumatic stress disorder.[99]

Current guidelines recommend implantation of an ICD under the following conditions:[100]

- goal-directed medical therapy has been tried for ≥3-6 months
- ≥40 days after MI
- expected survival >1 year
- patients with non-ischemic or ischemic HF with EF ≤35% and NYHA class II – III
- patients with ischemic (post-MI) HF with EF ≤30% and NYHA class I
- patients with ischemic HF and non-sustained ventricular tachycardia with EF ≤40%

Cardiac resynchronization therapy

Delays of the intraventricular conduction system occur in about one-third of patients with HFrEF, identifiable by a QRS duration of >120 milliseconds on ECG.[44] These patients may have left bundle

branch block (LBBB) or right bundle branch block (RBBB) on ECG. This conduction delay results in asynchronous contraction of the left and right ventricles, and resultant reduction of the cardiac output. Cardiac resynchronization therapy uses pacemaker leads placed in both ventricles to re-synchronize ventricular contraction.

CRT has been shown to prolong survival, reduce hospitalizations, and improve symptoms in patients with HFrEF who have cardiac dyssynchrony. The **CARE-HF trial** randomized 813 patients with HF due to LV systolic dysfunction and cardiac dyssynchrony to medical therapy alone or medical therapy plus CRT.[93] Patients in the CRT group had improved survival and symptoms and fewer HF hospitalizations (HR for relative reduction in death or hospitalization 0.63; 95% CI: 0.51-0.77, and HR for all-cause death 0.64; 95% CI: 0.48-0.85).

Patients with LBBB on ECG benefit more from CRT than patients with RBBB or non-LBBB on ECG. CRT can also improve LV systolic function and may reverse ventricular remodeling. Because effective CRT requires a high rate of ventricular pacing, the benefit for patients with AF is most evident in patients who have undergone atrioventricular nodal ablation or in patients with very good rate control.[1] Many patients who qualify for CRT will also benefit from an ICD. Such combination devices are referred to as cardiac resynchronization therapy with defibrillator (CRT-D).

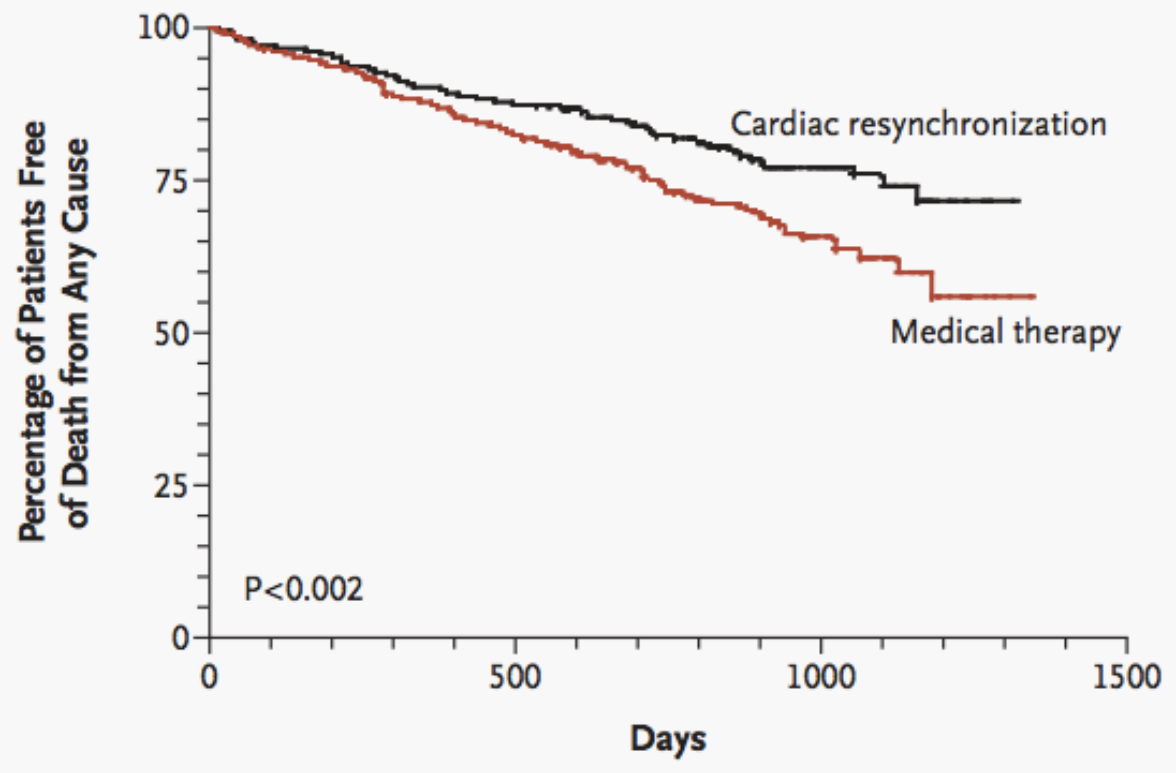
Table 19 summarizes the current guidelines for the use of CRT in patients with sinus rhythm, EF<35%, and on guideline-directed medical therapy.[1]

Table 19: Guidelines for CRT placement in patients with EF <35%[1]

Intraventricular conduction delay	QRS duration on ECG	
	120-149 msec	≥150 msec
LBBB	HF patients with NYHA class II-IV	HF patients with NYHA class II-IV
Non-LBBB	HF patients with NYHA class III-IV	HF patients with NYHA class III-IV

Patients with EF >35% and a narrow QRS may benefit from CRT if atrioventricular block is present and RV pacing is required more than 40% of the time. In such patients, biventricular pacing, compared to RV pacing alone, can reduce the risk of adverse cardiovascular events.[101] In the **BLOCK HF trial** patients with LVEF <50% and AVB randomized to CRT had a 26% lower risk of the composite endpoint of all-cause death, urgent HF visit, or ≥15% increase in LV volume.[101]

Figure 20: Survival improvement among CRT patients in CARE-HF trial[93]



BOTTOM LINE: ICDs are indicated as primary prevention in patients with EF <35% on maximal medical therapy (for a minimum of 3-6 months) with mild-severe HF symptoms. ICDs are also indicated in asymptomatic post-MI patients with EF <30%. CRT reduces morbidity and mortality in HFrEF patients with cardiac dyssynchrony. Patients with LBBB with a QRS duration >120 msec and mild-severe HF symptoms derive the most benefit. Patients with non-LBBB on ECG with a QRS duration >150 msec also benefit.

Additional interventions for HFrEF

Patients with HF often have other cardiac conditions that may be related to, or worsen, their HF symptoms. Referral to cardiology can help to manage the following:

- mitral regurgitation
- atrial fibrillation with difficult rate control
- coronary artery disease
- aortic stenosis

Transcatheter mitral valve repair (TMVR) is an option for patients with severe functional mitral regurgitation after maximal medical optimization. The device is percutaneously implanted via a transseptal approach. Evidence for efficacy is mixed. In the **COAPT trial** 614 patients with HF and mitral regurgitation were randomized to TMVR or standard care.[102] Patients in the device group had significantly lower rates of all-cause death at 24-month follow-up (HR 0.62; 95% CI: 0.46-0.82), cardiovascular death

(HR 0.59; 95% CI: 0.43-0.81), and HF hospitalization (HR 0.52; 95% CI: 0.40-0.67). The **MITRA-FR trial** (N=304) that also compared mitral-valve repair vs. a control group, however, found no significant differences in rates of death or unplanned HF hospitalization after 1 year follow-up.[103] Differences in outcomes may be related to patient selection and operator experience.

The most common arrhythmia in patients with HF is atrial fibrillation, which occurs in 30% to 40% of HF patients admitted to the hospital. Atrial fibrillation can exacerbate HF symptoms by reducing the "atrial kick", or amount of blood that fills the ventricle during diastole and atrial systole, and therefore the cardiac output. Although rhythm control has historically been recommended for patients with heart failure, the **AF-CHF trial** of patients with AF and HFrEF found no significant difference between rate and rhythm control for a range of clinical outcomes, including death from CV causes, death from any cause, stroke, worsening heart failure, and a composite of several of these outcomes.[104]

Atrial fibrillation (AF) that cannot be well-controlled with medication may be treated with catheter ablation. The **CASTLE-AF trial** randomized 398 patients with EF ≤35% and paroxysmal or persistent AF to either ablation or standard medical therapy.[105] Approximately one-third of patients in the medical therapy arm were treated with a rhythm-control strategy. The primary end point was a composite of death from any cause or hospitalization for worsening HF. After a median follow-up of 37.8 months, the primary composite end point occurred in significantly fewer patients in the ablation group than in the medical-therapy group (28.5% vs. 44.6%; HR 0.62; 95% CI: 0.43-0.87). Patients in the ablation group also had lower rates of death from any cause (HR 0.53; 95% CI: 0.32-0.86), hospitalization for worsening HF (HR 0.56; 95% CI: 0.37-0.83) or death from cardiovascular causes (HR 0.49; 95% CI: 0.29-0.84). The results should be interpreted cautiously because the patient population was highly selected, mortality in the control group may have been influenced by harm from antiarrhythmic drugs, and because of a high rate of cross-over between groups. The most recent AHA/ACC/HRS guidelines for AF, however, recommend ablation for symptomatic patients with HRrEF.[106]

Pharmacological management of HFpEF

As with patients with reduced EF, treatment goals for those with preserved EF are to improve symptoms, reduce volume overload, and treat hypertension and other comorbid conditions (e.g., atrial fibrillation and ischemic heart disease). Hypertension should be treated as recommended by current clinical guidelines, including treatment with diuretics, ACE inhibitors or ARBs, or calcium channel blockers.

Clinicians should be aware that excessive treatment poses risks in patients with symptomatic HFpEF because patients with a small, stiff left ventricle may be very sensitive to medications that reduce LV filling. Treatment with even standard dose diuretics or dihydropyridine calcium channel blockers may reduce preload and cause hypotension. Patients on these medications should be monitored for dizziness, syncope, and orthostatic hypotension.

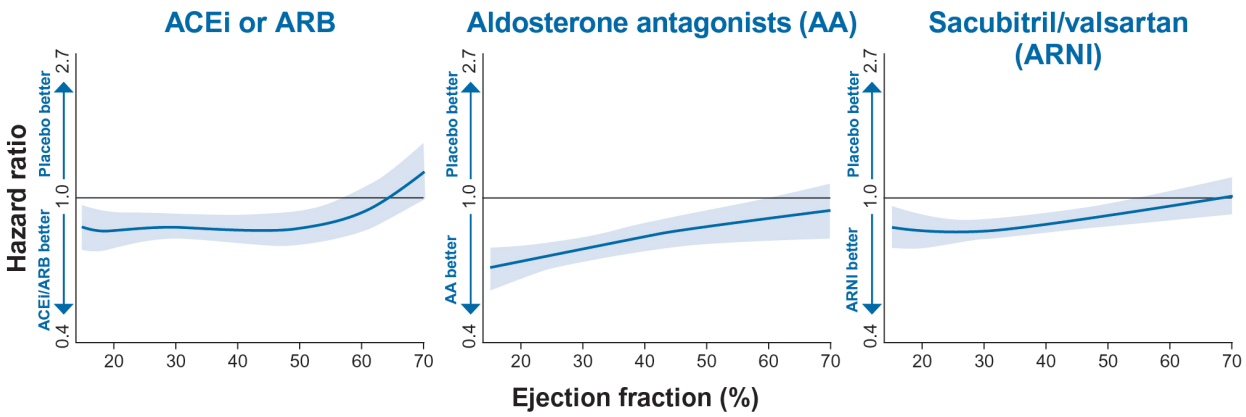
Medications that can improve survival in patients with reduced EF have generally *not* been effective in improving survival in patients with preserved EF.[107] The ACE inhibitor perindopril may reduce hospitalizations in patients with HFpEF, but the evidence is limited.[108] The **PEP-HF trial** randomized 852 patients with HFpEF to an ACE inhibitor or placebo, and found no difference in either the primary outcome (death or HF hospitalization) after 26 months, or most of the secondary outcomes.[108] Similarly, two RCTs of ARBs in HFpEF found no significant differences in outcomes.[109,52] The **CHARM-preserved trial** (N=3,023) found no differences in the composite outcome of CV death and HF hospitalization after

36 months.[109] The **I-PRESERVE trial** (N=4,128) also found no differences in the same composite outcome.[52]

In the 2014 **TOPCAT trial** (N=3,445) spironolactone was found to modestly lower the rate of hospitalization in patients with HFpEF (12% vs. 14.2%, p=0.04), a secondary endpoint, but patients on spironolactone had double the rate of hyperkalemia (18.7% vs. 9.1%)[110] suggesting that this agent may be useful in selected patients with close laboratory monitoring for hyperkalemia.

The **PARAGON-HF trial** evaluated the combination of sacubitril and valsartan in 4,796 patients with HFpEF who were randomized to either the combination or valsartan alone.[111] Non-significant reductions were observed for the composite of CV death and HF hospitalizations as well as in HF hospitalizations alone and CV death alone. Greater benefit was observed in patients with lower EF and in women. This general trend of greater benefit of neurohormonal blockade in patients with below-normal left ventricular function was also observed in an analysis of combined data from four clinical trials in patients with HFpEF (Figure 21).

Figure 21: Data from CHARM, TOPCAT, PARADIGM, and PARAGON trials show reduced risk of HF hospitalization and CV death with lower EF, but benefits continue for some patients with EF >40%.[112]



The **EMPEROR-Preserved trial** randomized 5,988 patients with class II-IV heart failure and an ejection fraction of more than 40% to the SGLT-2 inhibitor empagliflozin (10 mg/day) or placebo, in addition to usual therapy.[113] Over a median follow-up of 26.2 months, the primary outcome (composite of cardiovascular death or hospitalization for heart failure) occurred in 13.8% of the empagliflozin group vs. 17.1% in the placebo group (HR 0.79; 95% CI: 0.69-0.90). The effect was driven primarily by lower risk of hospitalization—no statistically significant differences in either cardiovascular death or death from any cause was observed. In addition, the benefit of empagliflozin was primarily in patients with ejection fractions of 40-50%. Hazard ratios for the primary outcome observed in sub-population analyses were clearly significant for patients with baseline LVEF 40-50% (HR 0.71; 95% CI: 0.57-088), marginally significant for patients with LVEF between 50% and 60% (HR 0.80; 95% CI: 0.64-0.99), and not significant for patients with LVEF ≥60% (HR 0.87; 95% CI: 0.69-1.10).

The findings from studies of beta blockers in patients with HFpEF have been modestly positive. The largest trial enrolled elderly patients recently hospitalized for HF (**SENIORS trial**) and randomized them to the beta blocker nebivolol or placebo.[114] The analysis found beneficial effects of nebivolol on all outcomes that were similar between the preserved and reduced EF groups; outcomes included mortality, CV

hospitalizations, HF hospitalizations, all-cause hospitalizations and sudden cardiac death (SCD).[114] More recent studies and analyses, however, suggest that the evidence for a benefit of beta blockers in patients with HFpEF is limited and very mixed.[115,116] Current guidelines do not recommend beta blocker use in these patients unless needed for another indication.

The only large randomized trial of digoxin in patients with HFpEF did not find any benefit on mortality or CV hospitalization.[117]

BOTTOM LINE: The benefits of medications for patients with HFpEF occur along a spectrum, with greater benefits for patients with lower EFs. Patients with mid-range EF (i.e., 41-49%) may be treated similarly to patients with HFrEF. Findings from trials of SGLT-2 inhibitors in patients with HFpEF suggest benefit. ARNIs and aldosterone antagonists may be beneficial, but beta blockers should be avoided unless needed for another indication.

Managing common comorbid conditions

Patients with HF often have many co-morbid conditions that can affect the management of their heart disease. According to Medicare claims data, about 40% of patients with HF have five or more co-morbid conditions.[118] Many older patients with HF are already taking multiple medications for their cardiac disease; the mean number of medications in all Medicare patients recently hospitalized for HF is 7, with a mean of 10 daily doses.[118] Therefore, careful attention must be paid to managing other co-morbid conditions without inducing unnecessary polypharmacy. This section will briefly discuss the most commonly associated co-morbid conditions, and how they impact the management of HF.

Hyperlipidemia

Two large randomized trials (**GISSI-HF trial** and the **CORONA trial**) in patients with symptomatic systolic HF found no benefit in any of the outcomes in patients randomized to rosuvastatin versus placebo.[119,120] There are no randomized trials of statin therapy in patients with HFpEF. Therefore statin therapy should not be initiated in HF patients for the purpose of improving outcomes, in the absence of other indications for statin therapy (e.g., primary prevention or ischemic heart disease).

Hypertension

Concomitant hypertension can worsen the symptoms of HF; blood pressure should be controlled at least to goal levels recommended by recent guidelines, i.e., BP<140/90 for most patients, and <130/80 in those with risk factors such as renal dysfunction.[121] Some recent studies suggest benefit for even lower targets.[122] Many medications used to treat HF are effective anti-hypertensives, including ACE inhibitors, ARBs, beta blockers, and diuretics.

Renal dysfunction

About 40% of HF patients also have chronic renal dysfunction, defined as creatinine clearance <60 mL/min.[118] This is often a consequence of low cardiac output and decreased renal perfusion with intrarenal vasoconstriction. About a third of patients admitted with HF have elevated serum creatinine

(e.g., >0.3 mg/dL over baseline), which is associated with higher morbidity and mortality compared to patients without such elevation.[123]

Many of the medications used to treat HF need to be adjusted for renal dysfunction. ACE inhibitors and ARBs both cause a transient reduction in creatinine clearance rates, although both are beneficial in patients with renal dysfunction -- especially when associated with proteinuria. The aldosterone antagonists should be used with caution in patients with renal dysfunction, with close monitoring of renal function and electrolytes (primarily potassium), and are contraindicated with creatinine clearance <10 mL/min. Doses of loop diuretics generally must be increased as the creatinine clearance decreases. The use of digoxin should be limited in those with renal dysfunction, and the dose should be appropriately decreased based on the creatinine clearance. Digoxin dosing calculators can help determine appropriate daily dosing. Beta blocker doses generally do not have to be adjusted for creatinine clearance, although atenolol, which is renally cleared, should be avoided.

BOTTOM LINE: comorbid conditions are common in patients with HF, complicating its management. Medications to be avoided include NSAIDS, non-dihydropyridine calcium channel blockers, and glitazones, all of which can worsen HF.

Hospitalization for acute HF exacerbation

A first HF hospitalization is an important prognostic event because the risk for readmission is 50% at 6 months and mortality is approximately 75% within 5 years. Factors that can precipitate acute HF include:

- poor adherence to medications and/or diet
- atrial fibrillation
- myocardial ischemia
- infection (pneumonia, UTI)
- new medications
  - increase fluid retention (NSAIDs)
  - negative inotropic agents (CCBs)
- excessive alcohol use
- uncontrolled hypertension
- pulmonary embolus
- thyroid disease
- worsening structural heart disease, such as mitral regurgitation

Several factors increase the need for hospitalization in HF, although individual differences in patients' functional status, home and caregiver situation, and resources will help shape the decision to admit or treat at home.

Table 20: Relative indications for hospital admission for HF[124]

HF symptoms with end-organ decompensation • hypoxia (oxygen saturation <90%) • altered mental status • worsening renal function
Worsened dyspnea, especially dyspnea at rest
Hypotension
New or hemodynamically significant arrhythmia (such as atrial fibrillation)
Major electrolyte abnormality
Significant weight gain (usually >5 kg above baseline) or worsening edema
Repeated ICD firings
Resistance to oral diuretics

Transitions of care are important and can help limit hospital readmission. HF patients who receive comprehensive discharge planning instead of usual care have:[125]

- 25% lower risk of hospital readmission
- trend towards lower mortality
- improved HF-related quality of life scores
- lower medical costs

Comprehensive planning may include:

- medication review and counseling by a pharmacist
- dietary counseling
- information about sodium and fluid restriction
- post-discharge home visits and/or telephone calls

Schedule follow-up visits relatively soon after discharge. Historically, nearly half of all readmissions occurred before the first post-discharge follow-up visit.[126] Medicare patients discharged from hospitals with high rates of early follow-up (i.e., within 7 days) have lower rates of 30-day readmission.[127] The following topics should be addressed during discharge follow-up visits:

- review and address reasons for HF exacerbation
- initiation of optimal medical therapy, if not done so already
- optimization of medication doses
- assessment of clinical status
- volume status (relative to discharge “dry weight”)
- renal function and electrolytes
- comorbid conditions
- HF education and self-care
- importance of medication adherence
- advanced directives

Advanced Heart Failure

Advanced HF (also called “end stage” or “refractory” HF) is characterized by:

- marked symptoms of dyspnea or fatigue at rest with minimal exertion despite optimal medical therapy (e.g., persistent dyspnea while dressing or bathing, inability to walk 1 block due to dyspnea or fatigue)
- intolerance to medical therapy
- escalating diuretic doses (furosemide doses >160 mg/d)
- frequent hypotension (SBP <90 mm Hg)
- frequent ICD shocks
- ≥2 hospitalizations or ED visits for HF in past year
- worsening renal function
- worsening serum sodium (<133 mEq/L)

In patients presenting with symptoms suggesting advanced HF, assess for other potential causes that can exacerbate HF or mimic HF symptoms, such as ischemic heart disease, concomitant pulmonary disease, sleep disordered breathing, and thyroid disorders.

The goals in treating advanced HF are to control symptoms, improve quality of life, reduce hospital admissions and identify the patient’s end-of-life goals (advance care directives should be discussed with all patients). In addition to the HF management strategies appropriate for earlier stages of HF, the following treatment options or management approaches should be considered for patients with advanced HF:

- chronic inotropes
- mechanical circulatory support (MCS) device (e.g., left ventricular assist devices)
- heart transplant
- palliative care and hospice

The following conditions or situations may warrant referral to a cardiologist or an HF specialist:[25]

- end-organ dysfunction
- EF ≤35%
- edema despite escalating diuretics
- progressive intolerance to guideline-directed medical therapy

Inotropic support

Inotropes (e.g., dobutamine and milrinone) are medications that increase cardiac contractility. Other positive inotropic agents increase the concentration of intracellular cyclic AMP, either by promoting its synthesis (beta-adrenergic agonists) or by retarding its degradation (phosphodiesterase inhibitors). The use of cyclic AMP—enhancing agents has been viewed as a particularly rational approach to the treatment of advanced heart failure, since the production of cyclic AMP is deficient in failing human hearts. Long-term use of infused inotropic drugs (and oral milrinone) increases mortality and hospitalizations, hence their use is reserved for:[128,129]

- patients hospitalized for cardiogenic shock

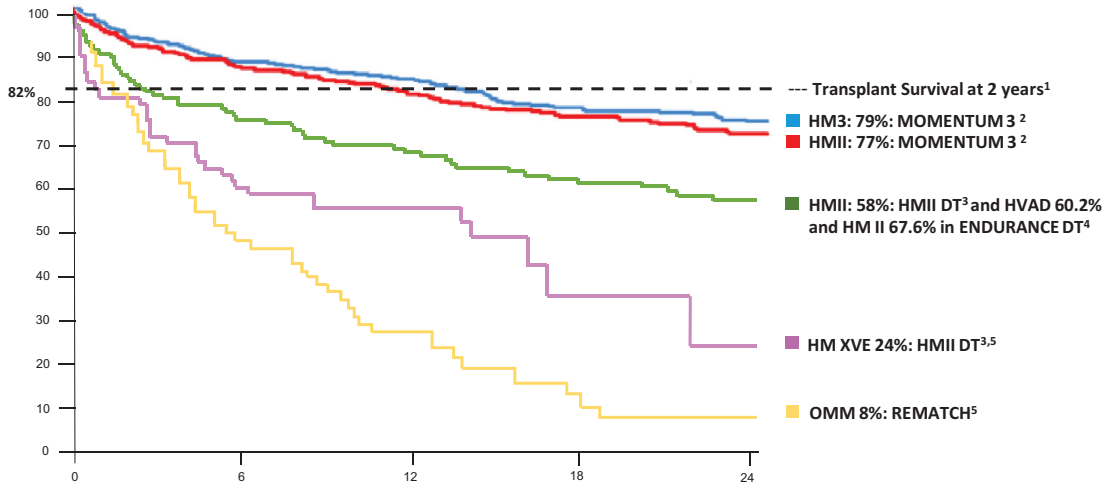
- “bridge” therapy for patients awaiting mechanical circulatory support (MCS) or heart transplant
- inpatient or outpatient palliation

Mechanical circulatory support

The most common type of MCS for patients with advanced HF is ventricular assist devices (VADs), which are mechanical pumps that bypass the ventricle. VADs can support the left ventricle (LVAD) the right ventricle (RVAD) or both (BiVAD) and can be used short- or long-term, either with percutaneous placement or as implants.

LVADs can be used either as a bridge to candidacy for heart transplant or as a destination therapy to improve survival and enhance quality of life. When used as a destination therapy they have been shown to improve the survival of patients with end-stage HF. Early types of LVAD devices improved survival by 48% compared to medical therapy alone.[130] New LVADs using a continuous flow have demonstrated survival rates of 80% at 1 year and 70% at 2 years.[131] Survival rates continue to improve with advancements in technology and medical care (Figure 22).

Figure 22: Evolving trends in survival with different LVADs at two years[132]



Note that, in general, patients getting LVADs live longer, but have higher rates of complications such as bleeding, pump thrombosis, systemic emboli, driveline infection, aortic insufficiency, and right heart failure.[133]

Heart transplant

Heart transplant is a last resort for patients with HF and refractory symptoms. About 3500 heart transplants are performed annually in the U.S., with an average 5-year survival rate of >70%.[134] The one-year survival of patients on the waiting list has improved from 34% (1987-1990) to 68% (2011-2017).[135] Patients must be carefully screened for their ability to endure the surgery, and to emotionally and logistically comply with all post-transplant medications and other therapies. Given the scarcity of heart donors, many patients may need placement of a mechanical circulatory support (MCS) device while waiting for a donor heart.

Common contraindications to transplant include:

- fixed pulmonary hypertension
- severe symptomatic cerebrovascular disease
- active tobacco or illicit substance use
- advanced age

Palliative care in advanced HF

Palliative care is specialized medical care for people with serious illness focused on relieving symptoms and improving quality of life for both the patient and the family throughout the course of an illness and which is integrated with disease treatments. Structured palliative care interventions may improve quality of life, depression, anxiety, and a patient's understanding of his or her prognosis.[136] Palliative care team members should be involved early in treatment for HF, and palliative care measures should not be reserved for the final months or weeks of a patient's life (Table 21).

Table 21: Palliative management of advanced HF symptoms[137]

Symptoms	First-line therapy	Alternative therapies
Dyspnea	• diuretics • nitrates • low-dose opioids	• inotropies • aquapheresis • breathing training • exercise training • oxygen
Pain	• opioids • bisphosphonates (for bone pain) • nitrates, beta blockers, calcium channel blockers, ranolazine, catheterization (for angina pain)	• exercise training
Depression	Antidepressants • selective serotonin reuptake inhibitors • serotonin-norepinephrine reuptake inhibitors • tricyclic antidepressants	Counseling
Fatigue	Treat secondary causes	Stimulants Exercise training

An analysis of Medicare beneficiaries found that 80% of those with HF were hospitalized within the last 6 months of life, with a significant increase in ICU days and overall costs during the last 6 months of life. However, the same analysis found the use of hospice increased from 19% of patients (before the last 6 months of life) to 40% of patients (within the last 6 months of life).[138] End-of-life care discussions should involve the following topics:[16]

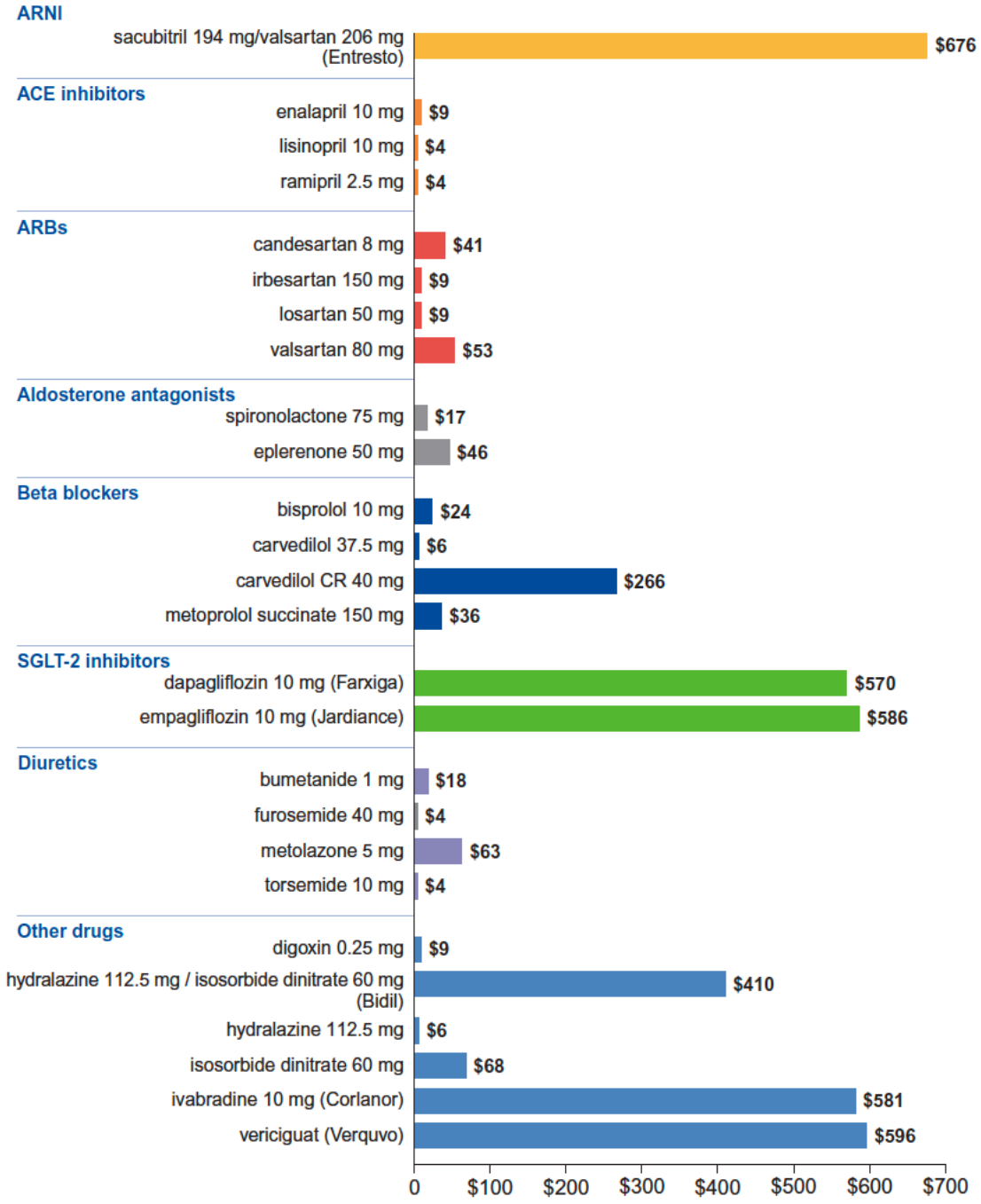
- symptomatic therapy for dyspnea (including oxygen therapy)
- symptomatic therapy for anxiety or depression (if present)
- information on how to prepare a medical power of attorney, living will, and "do not resuscitate" orders

- the potential futility of invasive management at the end of life (e.g., ICUs, ventilators, cardiac resuscitation)
- potential benefits of hospice care (at home or in a facility)
- ICD inactivation (if present).

Initiation of discussions about patient wishes for end of life care can also be helpful for patients at less advanced stages of HF, allowing them time to consider their preferences and discuss their decisions with family members and/or a health care proxy.

Costs

Figure 23: Cost of a 30-day supply of medications used in managing heart failure



Prices from goodrx.com, June 2021. Listed doses are based on Defined Daily Doses by the World Health Organization and should not be used for dosing in all patients. All doses shown are generics when available, unless otherwise noted. These prices are a guide; patient costs will be subject to copays, rebates, and other incentives.

Putting it all together

All patients with HF should be treated for risk factors that can exacerbate their disease (e.g., hypertension, diabetes, and atrial fibrillation), and prescribed a diuretic if needed to reduce volume overload.

Non-pharmacologic therapy for all HF patients should consist of sodium and fluid restriction, commensurate with the degree of symptoms and edema. Patients should avoid smoking and alcohol, and be educated on vaccines, and exercise. Co-morbid conditions are common and should be carefully addressed to avoid polypharmacy and drug interactions. Acute exacerbations should be managed with diuretics, with more aggressive interventions reserved for unstable patients. Patient education is an important component of HF care, and should include planning for end of life care in class IV patients.

Even after HF hospitalization many patients aren't prescribed life-saving medications, and most are not taking optimal doses. After hospitalization, address non-adherence concerns, review weight goals and salt or fluid restriction, and refer for cardiac rehabilitation.

HFrEF patients

- comprehensive medical and device therapy reduces morbidity and mortality.
- SGLT-2 inhibitors provide benefit regardless of diabetes diagnosis.
- sacubitril/valsartan (Entresto) should be a first-line treatment in most patients with symptomatic HF (unless cost prohibitive or therapy not tolerated).
- initiate sacubitril/valsartan, a beta-blocker, and an aldosterone antagonist, titrated to maximally tolerated dose, and an SGLT-2 inhibitor.
- continue medications prescribed for HFrEF even if ejection fraction improves ≥10% to >40%.
- mortality and morbidity benefits for HF medications are best at the higher doses used in the original studies. However, a lower dose is better than not receiving treatment in patients who are unable to tolerate higher doses.
- the combination of hydralazine with isosorbide dinitrate may be particularly appropriate for Black patients; ivabradine and vericiguat, when indicated, and possibly digoxin may be an option in all patients to lower the risk of HF hospitalization.
- invasive therapies, including ICDs, CRT, MCS, and transplantation, should be considered depending on the patient's clinical status, ejection fraction and QRS duration.
- discuss the goals of care and advance care directives for patients with severe, end-stage HF.
- involve palliative care team members early in disease process.

HFpEF patients

- no therapies improve survival, but aldosterone antagonists, SGLT-2 inhibitors, and sacubitril/valsartan may offer benefits in selected patients to reduce HF hospitalizations
- for those with HFpEF, guidelines recommend the following medications to reduce volume overload and hypertension, generally in this order:
  - diuretics (thiazide or loop)
  - ACE inhibitor or ARB (especially with prior MI, CAD, or diabetes)
  - beta blocker (especially with prior MI, CAD, angina or atrial fibrillation)
- discuss the goals of care and advance care directives for patients with severe, end-stage HF.
- involve palliative care team members early in disease process.

References

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* 2013;128(16):e240-327.
2. Tzanetos K, Leong D, Wu RC. Office management of patients with diastolic heart failure. *Cmaj.* 2009;180(5):520-527.
3. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail.* 2021;23(3):352-380.
4. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation.* 2021;143(8):e254-e743.
5. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation.* 2014;129(3):e28-e292.
6. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA.* 2004;292(3):344-350.
7. Shah KS, Xu H, Matsouaka RA, et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol.* 2017;70(20):2476-2486.
8. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. *JAMA.* 2011;306(15):1669-1678.
9. Bergethon KE, Ju C, DeVore AD, et al. Trends in 30-Day Readmission Rates for Patients Hospitalized With Heart Failure: Findings From the Get With The Guidelines-Heart Failure Registry. *Circ Heart Fail.* 2016;9(6).
10. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail.* 2013;6(3):606-619.
11. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National Burden of Heart Failure Events in the United States, 2006 to 2014. *Circ Heart Fail.* 2018;11(12):e004873.
12. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation.* 2002;106(24):3068-3072.
13. Agarwal SK, Chambless LE, Ballantyne CM, et al. Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) Study. *Circ Heart Fail.* 2012;5(4):422-429.
14. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2019;73(22):2872-2891.
15. National Guideline Clearinghouse. Guideline synthesis: Diagnosis and evaluation of chronic heart failure (CHF). 2010.
16. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation.* 2005;112(12):e154-235.
17. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J.* 2006;27(3):330-337.
18. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med.* 2002;347(3):161-167.
19. Anand IS, Fisher LD, Chiang YT, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). *Circulation.* 2003;107(9):1278-1283.
20. Lainchbury JG, Troughton RW, Strangman KM, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol.* 2009;55(1):53-60.
21. Porapakkham P, Porapakkham P, Zimmet H, Billah B, Krum H. B-type natriuretic peptide-guided heart failure therapy: A meta-analysis. *Arch Intern Med.* 2010;170(6):507-514.
22. Troughton RW, Frampton CM, Brunner-La Rocca HP, et al. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. *Eur Heart J.* 2014;35(23):1559-1567.
23. Felker GM, Anstrom KJ, Adams KF, et al. Effect of Natriuretic Peptide-Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA.* 2017;318(8):713-720.

24. Kato ET, Silverman MG, Mosenzon O, et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. *Circulation.* 2019;139(22):2528-2536.
25. Maddox TM, Januzzi JL, Jr., Allen LA, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;77(6):772-810.
26. Conn VS, Ruppar TM. Medication adherence outcomes of 771 intervention trials: Systematic review and meta-analysis. *Prev Med.* 2017;99:269-276.
27. Gilmour J, Strong A, Chan H, Hanna S, Huntington A. Primary health care nurses and heart failure education: a survey. *J Prim Health Care.* 2014;6(3):229-237.
28. Rice H, Say R, Betihavas V. The effect of nurse-led education on hospitalisation, readmission, quality of life and cost in adults with heart failure. A systematic review. *Patient Educ Couns.* 2018;101(3):363-374.
29. Maric B, Kaan A, Ignaszewski A, Lear SA. A systematic review of telemonitoring technologies in heart failure. *Eur J Heart Fail.* 2009;11(5):506-517.
30. Gupta D, Georgiopoulou VV, Kalogeropoulos AP, et al. Dietary sodium intake in heart failure. *Circulation.* 2012;126(4):479-485.
31. MacDonald M, Fang J, Pittman SD, White DP, Malhotra A. The current prevalence of sleep disordered breathing in congestive heart failure patients treated with beta-blockers. *J Clin Sleep Med.* 2008;4(1):38-42.
32. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med.* 2005;353(19):2025-2033.
33. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. *N Engl J Med.* 2015;373(12):1095-1105.
34. Ades PA, Keteyian SJ, Balady GJ, et al. Cardiac rehabilitation exercise and self-care for chronic heart failure. *JACC Heart Fail.* 2013;1(6):540-547.
35. Golwala H, Pandey A, Ju C, et al. Temporal Trends and Factors Associated With Cardiac Rehabilitation Referral Among Patients Hospitalized With Heart Failure: Findings From Get With The Guidelines-Heart Failure Registry. *J Am Coll Cardiol.* 2015;66(8):917-926.
36. Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. *Eur J Heart Fail.* 2005;7(3):411-417.
37. Forman DE, Sanderson BK, Josephson RA, Raikhelkar J, Bittner V, American College of Cardiology's Prevention of Cardiovascular Disease S. Heart Failure as a Newly Approved Diagnosis for Cardiac Rehabilitation: Challenges and Opportunities. *J Am Coll Cardiol.* 2015;65(24):2652-2659.
38. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev.* 2014;4:CD003331.
39. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA.* 2009;301(14):1439-1450.
40. Gary RA, Sueta CA, Dougherty M, et al. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. *Heart Lung.* 2004;33(4):210-218.
41. Kitzman DW, Whellan DJ, Duncan P, et al. Physical Rehabilitation for Older Patients Hospitalized for Heart Failure. *N Engl J Med.* 2021;385(3):203-216.
42. Eisenberg MJ, Grandi SM, Gervais A, et al. Bupropion for smoking cessation in patients hospitalized with acute myocardial infarction: a randomized, placebo-controlled trial. *J Am Coll Cardiol.* 2013;61(5):524-532.
43. Svanstrom H, Pasternak B, Hviid A. Use of varenicline for smoking cessation and risk of serious cardiovascular events: nationwide cohort study. *BMJ.* 2012;345:e7176.
44. McMurray JJ. Clinical practice. Systolic heart failure. *The New England journal of medicine.* 2010;362(3):228-238.
45. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol.* 2002;82(2):149-158.
46. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;75(10):1178-1195.
47. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). . *N Engl J Med.* 1987;316(23):1429-1435.
48. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. . *N Engl J Med.* 1991;325(5):293-302.
49. The SOLVD Investigattors. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. . *N Engl J Med.* 1992;327(10):685-691.
50. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med.* 2001;344(18):1351-1357.

51. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation.* 1999;100(23):2312-2318.
52. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med.* 2008;359(23):2456-2467.
53. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet.* 2003;362(9386):772-776.
54. Cohn JN, Tognoni G, Valsartan Heart Failure Trial I. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med.* 2001;345(23):1667-1675.
55. Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. *Cochrane Database Syst Rev.* 2012;4:CD003040.
56. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet.* 2009;374(9704):1840-1848.
57. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet.* 2003;362(9386):759-766.
58. Swedberg K. Heart failure therapies in 2014: Mixed results for heart failure therapies. *Nat Rev Cardiol.* 2015;12(2):73-75.
59. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371(11):993-1004.
60. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. *N Engl J Med.* 2019;380(6):539-548.
61. MERIT-HF study group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999;353(9169):2001-2007.
62. CIBIS-II investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353(9146):9-13.
63. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation.* 1996;94(11):2807-2816.
64. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet.* 2003;362(9377):7-13.
65. Bonet S, Agusti A, Arnau JM, et al. Beta-adrenergic blocking agents in heart failure: benefits of vasodilating and non-vasodilating agents according to patients' characteristics: a meta-analysis of clinical trials. *Arch Intern Med.* 2000;160(5):621-627.
66. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *The New England journal of medicine.* 2001;344(22):1651-1658.
67. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med.* 1999;341(10):709-717.
68. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348(14):1309-1321.
69. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med.* 2011;364(1):11-21.
70. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med.* 2004;351(6):543-551.
71. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;75(4):422-434.
72. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med.* 2019;381(21):1995-2008.
73. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med.* 2020;383(15):1413-1424.
74. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet.* 2020;396(10254):819-829.
75. Cole RT, Kalogeropoulos AP, Georgiopoulou VV, et al. Hydralazine and isosorbide dinitrate in heart failure: historical perspective, mechanisms, and future directions. *Circulation.* 2011;123(21):2414-2422.
76. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med.* 1991;325(5):303-310.
77. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med.* 2004;351(20):2049-2057.

78. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376(9744):875-885.
79. Corlanor Full Prescribing Information. Amgen Inc. Thousand Oaks CIA, 2015.
80. Digitalis Investigation G. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med.* 1997;336(8):525-533.
81. Turakhia MP, Santangeli P, Winkelmayer WC, et al. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. *J Am Coll Cardiol.* 2014;64(7):660-668.
82. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med.* 2020;382(20):1883-1893.
83. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med.* 2021;384(2):129-139.
84. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med.* 2021;384(2):117-128.
85. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet.* 2020;396(10244):121-128.
86. Srivastava PK, Claggett BL, Solomon SD, et al. Estimated 5-Year Number Needed to Treat to Prevent Cardiovascular Death or Heart Failure Hospitalization With Angiotensin Receptor-Neprilysin Inhibition vs Standard Therapy for Patients With Heart Failure With Reduced Ejection Fraction: An Analysis of Data From the PARADIGM-HF Trial. *JAMA Cardiol.* 2018;3(12):1226-1231.
87. Packer M. What causes sudden death in patients with chronic heart failure and a reduced ejection fraction? *Eur Heart J.* 2020;41(18):1757-1763.
88. Cupples LA, Gagnon DR, Kannel WB. Long- and short-term risk of sudden coronary death. *Circulation.* 1992;85(1 Suppl):I11-18.
89. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med.* 2005;352(3):225-237.
90. Chang PM, Doshi R, Saxon LA. Subcutaneous implantable cardioverter-defibrillator. *Circulation.* 2014;129(23):e644-646.
91. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346(12):877-883.
92. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;350(21):2140-2150.
93. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005;352(15):1539-1549.
94. Santangeli P, Di Biase L, Dello Russo A, et al. Meta-analysis: age and effectiveness of prophylactic implantable cardioverter-defibrillators. *Ann Intern Med.* 2010;153(9):592-599.
95. Kramer DB, Matlock DD, Buxton AE, et al. Implantable Cardioverter-Defibrillator Use in Older Adults: Proceedings of a Hartford Change AGEnts Symposium. *Circ Cardiovasc Qual Outcomes.* 2015;8(4):437-446.
96. Alter P, Waldhans S, Plachta E, Moosdorf R, Grimm W. Complications of implantable cardioverter defibrillator therapy in 440 consecutive patients. *Pacing Clin Electrophysiol.* 2005;28(9):926-932.
97. Koneru JN, Jones PW, Hammill EF, Wold N, Ellenbogen KA. Risk Factors and Temporal Trends of Complications Associated With Transvenous Implantable Cardiac Defibrillator Leads. *J Am Heart Assoc.* 2018;7(10).
98. Ezzat VA, Lee V, Ahsan S, et al. A systematic review of ICD complications in randomised controlled trials versus registries: is our 'real-world' data an underestimation? *Open Heart.* 2015;2(1):e000198.
99. Sears SF, Hauf JD, Kirian K, Hazelton G, Conti JB. Posttraumatic stress and the implantable cardioverter-defibrillator patient: what the electrophysiologist needs to know. *Circ Arrhythm Electrophysiol.* 2011;4(2):242-250.
100. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2018;138(13):e272-e391.
101. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med.* 2013;368(17):1585-1593.
102. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N Engl J Med.* 2018;379(24):2307-2318.
103. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N Engl J Med.* 2018;379(24):2297-2306.
104. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med.* 2008;358(25):2667-2677.
105. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med.* 2018;378(5):417-427.

106. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation.* 2019;140(2):e125-e151.
107. Oghlakian GO, Sipahi I, Fang JC. Treatment of heart failure with preserved ejection fraction: have we been pursuing the wrong paradigm? *Mayo Clin Proc.* 2011;86(6):531-539.
108. Cleland JG, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J.* 2006;27(19):2338-2345.
109. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet.* 2003;362(9386):777-781.
110. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* 2014;370(15):1383-1392.
111. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med.* 2019;381(17):1609-1620.
112. Dewan P, Jackson A, Lam CSP, et al. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail.* 2020;22(5):898-901.
113. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *New England Journal of Medicine.* 2021.
114. van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol.* 2009;53(23):2150-2158.
115. Martin N, Manoharan K, Thomas J, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. *Cochrane Database Syst Rev.* 2018;6:CD012721.
116. Joseph P, Swedberg K, Leong DP, Yusuf S. The Evolution of beta-Blockers in Coronary Artery Disease and Heart Failure (Part 1/5). *J Am Coll Cardiol.* 2019;74(5):672-682.
117. Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation.* 2006;114(5):397-403.
118. Lang CC, Mancini DM. Non-cardiac comorbidities in chronic heart failure. *Heart.* 2007;93(6):665-671.
119. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med.* 2007;357(22):2248-2261.
120. Ghio S, Scelsi L, Latini R, et al. Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial. *Eur J Heart Fail.* 2010;12(12):1345-1353.
121. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension.* 2020;75(6):1334-1357.
122. Landmark NIH study shows intensive blood pressure management may save lives [press release]. September 11, 2015.
123. Cotter G, Felker GM, Adams KF, Milo-Cotter O, O'Connor CM. The pathophysiology of acute heart failure--is it all about fluid accumulation? *Am Heart J.* 2008;155(1):9-18.
124. Onwuanyi A, Taylor M. Acute decompensated heart failure: pathophysiology and treatment. *Am J Cardiol.* 2007;99(6B):25D-30D.
125. Phillips CO, Wright SM, Kern DE, Singa RM, Shepperd S, Rubin HR. Comprehensive discharge planning with postdischarge support for older patients with congestive heart failure: a meta-analysis. *JAMA.* 2004;291(11):1358-1367.
126. Lee DS, Stukel TA, Austin PC, et al. Improved outcomes with early collaborative care of ambulatory heart failure patients discharged from the emergency department. *Circulation.* 2010;122(18):1806-1814.
127. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. *JAMA.* 2010;303(17):1716-1722.
128. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med.* 1991;325(21):1468-1475.
129. Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol.* 2005;46(1):57-64.
130. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med.* 2001;345(20):1435-1443.
131. Fang JC. Rise of the machines--left ventricular assist devices as permanent therapy for advanced heart failure. *N Engl J Med.* 2009;361(23):2282-2285.
132. Sidhu K, Lam PH, Mehra MR. Evolving trends in mechanical circulatory support: Clinical development of a fully magnetically levitated durable ventricular assist device. *Trends Cardiovasc Med.* 2020;30(4):223-229.
133. Han JJ, Acker MA, Atluri P. Left Ventricular Assist Devices. *Circulation.* 2018;138(24):2841-2851.

134. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. *J Heart Lung Transplant.* 2016;35(1):1-23.
135. Bakhtiyar SS, Godfrey EL, Ahmed S, et al. Survival on the Heart Transplant Waiting List. *JAMA Cardiol.* 2020;5(11):1227-1235.
136. Chuzi S, Pak ES, Desai AS, Schaefer KG, Warraich HJ. Role of Palliative Care in the Outpatient Management of the Chronic Heart Failure Patient. *Curr Heart Fail Rep.* 2019;16(6):220-228.
137. Adler ED, Goldfinger JZ, Kalman J, Park ME, Meier DE. Palliative care in the treatment of advanced heart failure. *Circulation.* 2009;120(25):2597-2606.
138. Unroe KT, Greiner MA, Hernandez AF, et al. Resource use in the last 6 months of life among medicare beneficiaries with heart failure, 2000-2007. *Arch Intern Med.* 2011;171(3):196-203.

About this publication

These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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