Pharmacotherapy 1

Heart Failure

(Updated March 2026; **updates are in RED**)

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Topic outline:

- ✓ Definition
- ✓ Epidemiology
- ✓ Etiology
- ✓ Normal Cardiac Function
- ✓ Pathophysiology
- ✓ Factors Precipitating/Exacerbating Heart Failure
- ✓ Clinical Presentation
- ✓ Laboratory Tests
- ✓ Diagnosis
- ✓ Treatment of Chronic Heart Failure

➢ Definition

- ✓ Heart failure (HF) is a progressive clinical syndrome caused by inability of the heart to pump sufficient blood to meet the body's metabolic needs.

- ✓ HF can result from any abnormality in cardiac structure or function that impairs the ability of the ventricle to fill with (diastolic dysfunction) or eject blood (systolic dysfunction).

- ✓ Diastolic dysfunction (restriction in ventricular filling): HF with preserved LVEF (HFpEF) or normal systolic function (normal LVEF)- patients typically are elderly, female, and obese, and have HTN, atrial fibrillation, or diabetes.

- ✓ Systolic dysfunction (decreased contractility): HF with reduced ejection fraction (HFrEF)- the classic, more familiar form of the disorder and is often caused by previous MI

TABLE 39-1

Classification of Heart Failure According to Left Ventricular Ejection Fraction

HF with reduced EF (HFrEF)	HF with LVEF ≤40% (0.4)
HF with mildly reduced EF (HFmrEF)	HF with LVEF 41%-49% (0.41-0.49)
HF with preserved EF (HFpEF)	HF with LVEF ≥50% (0.5)
HF with improved EF (HFimpEF)	HF with baseline LVEF ≤40% (0.4) and subsequent measurement of LVEF >40% (0.4)

➢ Epidemiology

- ✓ In Jordan, the prevalence of HF is approximately 100,000; the estimated incidence is 8251 annually *
- ✓ Improved survival after MI → increased incidence & prevalence of HF
- ✓ Current estimates of annual expenditures for HF: > $30 billion (mainly on hospitalized patients)
- ✓ The overall 5-year survival is approximately 42% for all patients with a diagnosis of HF.
- ✓ Death is classified as sudden in about 40% of patients, due to serious ventricular arrhythmias as the underlying cause.

*: Abu Hayeah, Haneen & Saifan, Ahmad & Aburuz, Mohannad & Aljabery, Mohannad. (2017). Health-Related Quality of Life in Heart Failure in Jordan from Patients perspectives. IOSR Journal of Nursing and Health Science. 06. 14-21. 10.9790/1959-0601031421.

➢ Etiology

✓ The most common causes of HF are:

- CAD resulting in an acute MI (75% of cases)
- HTN
- Cardiomyopathies

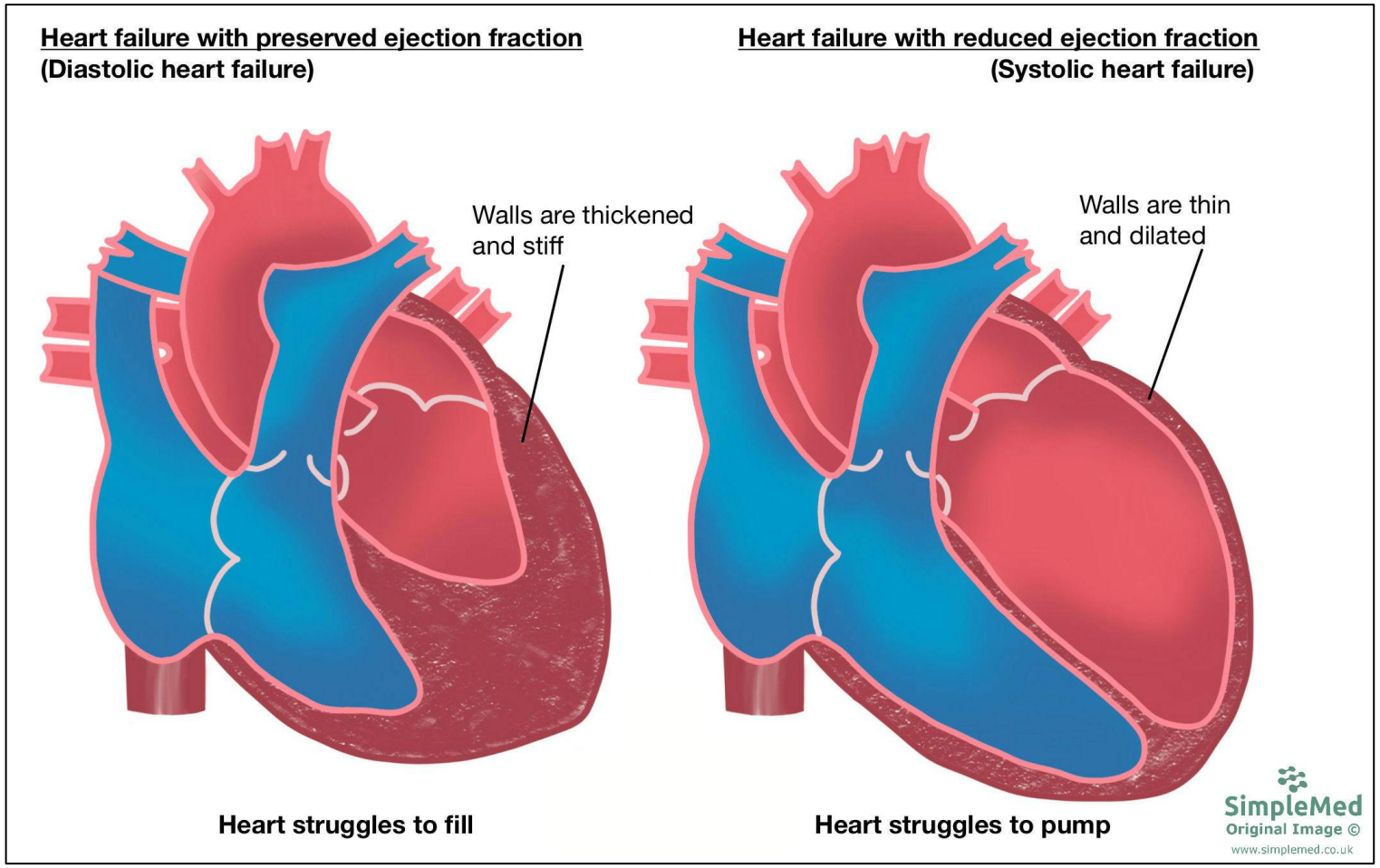


TABLE 39-2

Common Causes of Chronic Heart Failure

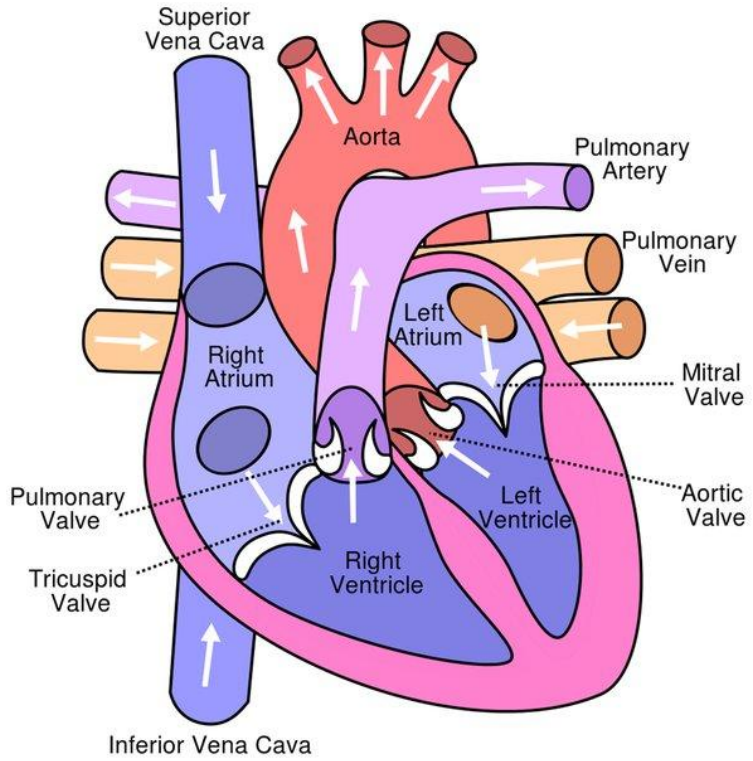
CAD (eg, myocardial infarction [MI] or ischemia)
HTN
Metabolic disorders (eg, obesity, diabetes)
Valvular heart disease (eg, aortic stenosis)
Heart rhythm disorders (eg, AF, tachycardia-induced cardiomyopathy)
Chemotherapy and other cardiotoxic medications (eg, alcohol, stimulants)
Infiltrative myocardial disease (eg, amyloidosis, sarcoidosis)
Dilated cardiomyopathies (eg, genetic heart disease, viral infections, peripartum)
Pericardial disease (eg, pericarditis, pericardial tamponade)
Ventricular hypertrophy (eg, hypertrophic cardiomyopathy [HCM])

➢ Normal Cardiac Function

✓ CO is the volume of blood ejected per unit time (L/min) and is the product of HR & SV

$CO = HR \times SV$ $BP = CO \times$ systemic vascular resistance (SVR)

✓ SV, or the volume of blood ejected during systole, depends on **preload**, **afterload**, & **contractility**.



➢ Compensatory Mechanisms in HFrEF

- ✓ HFrEF is a progressive disorder initiated by any event that impairs the ability of the heart to contract resulting in a decrease in CO.
- ✓ A decrease in CO results in activation of compensatory responses to maintain the circulation.
- ✓ Compensatory responses evolved to provide short-term support to maintain circulatory homeostasis after acute reductions in BP or renal perfusion.
- ✓ The persistent decline in CO in HF triggers long-term activation of these compensatory responses resulting in the complex functional, structural, biochemical, and molecular changes important for the development and progression of HF.

✓ Compensatory mechanisms:

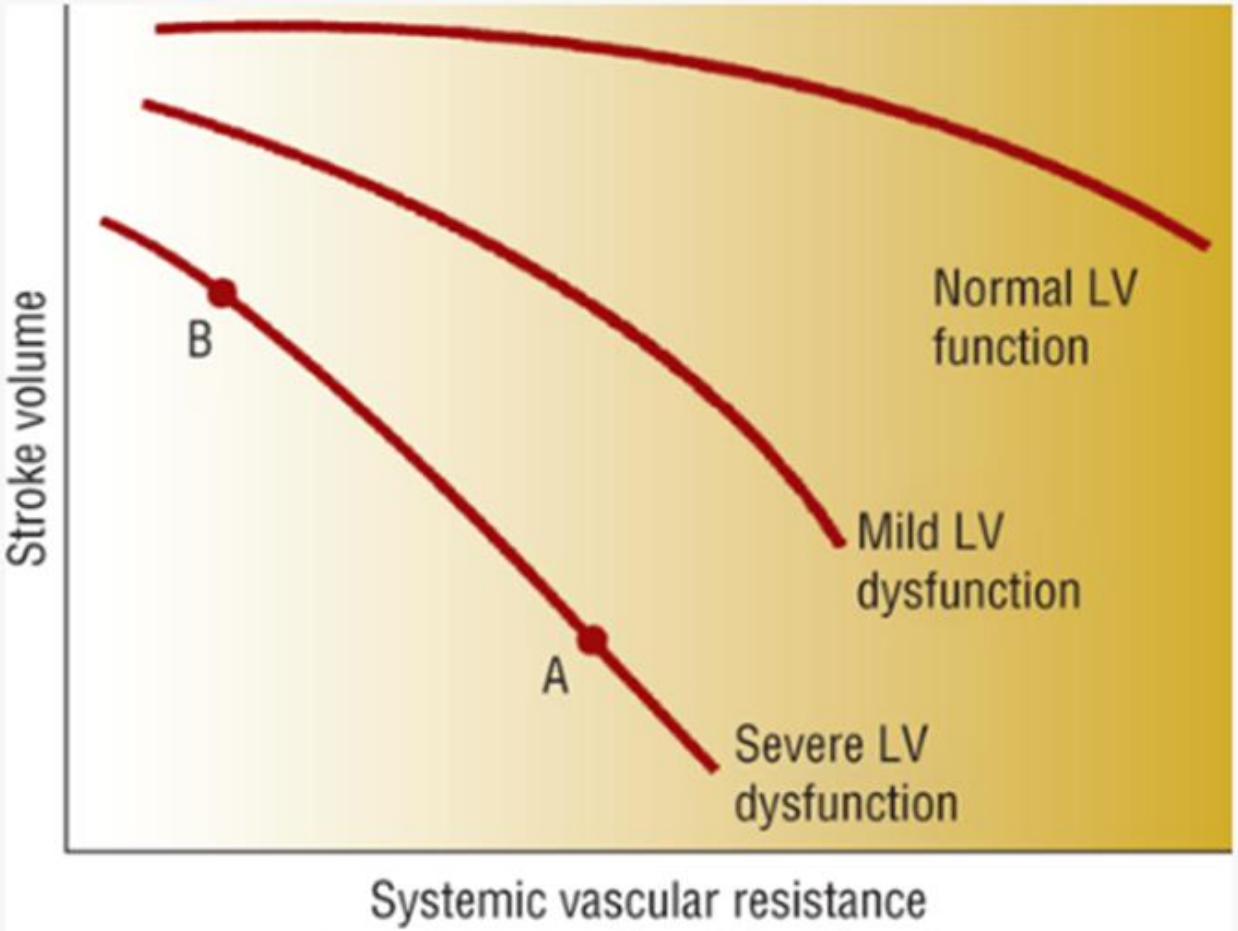
1. Tachycardia and increased contractility (sympathetic nervous system activation)
2. The Frank–Starling mechanism (increased preload increases stroke volume)
3. Vasoconstriction
4. Ventricular hypertrophy and remodelling

✓ Our current understanding of HFrEF pathophysiology is best described by the neurohormonal model. Activation of endogenous neurohormones including norepinephrine (NE), angiotensin II, aldosterone and numerous proinflammatory cytokines plays an important role in ventricular remodeling and the subsequent progression of HF.

✓ Importantly, pharmacotherapy targeted at antagonizing this neurohormonal activation has slowed the progression of HFrEF and improved survival.

Figure 39-1 Relationship between stroke volume and systemic vascular resistance.

In an individual with normal left ventricular (LV) function, increasing systemic vascular resistance has little effect on stroke volume. As the extent of LV dysfunction increases, the negative, inverse relationship between stroke volume and systemic vascular resistance becomes more important (B to A).



Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

Figure 39-2 Physiology of the renin-angiotensin-aldosterone system.

Renin converts angiotensinogen to angiotensin I (AT1). AT1 is cleaved to angiotensin II (AT2) by the angiotensin-converting enzyme (ACE). AT2 has a number of physiologic actions that are detrimental in HF. Note that AT2 can be produced in a number of tissues, including the heart, independent of ACE activity. ACE is also responsible for the breakdown of bradykinin. Inhibition of ACE results in the accumulation of bradykinin that, in turn, enhances the production of vasodilatory prostaglandins.

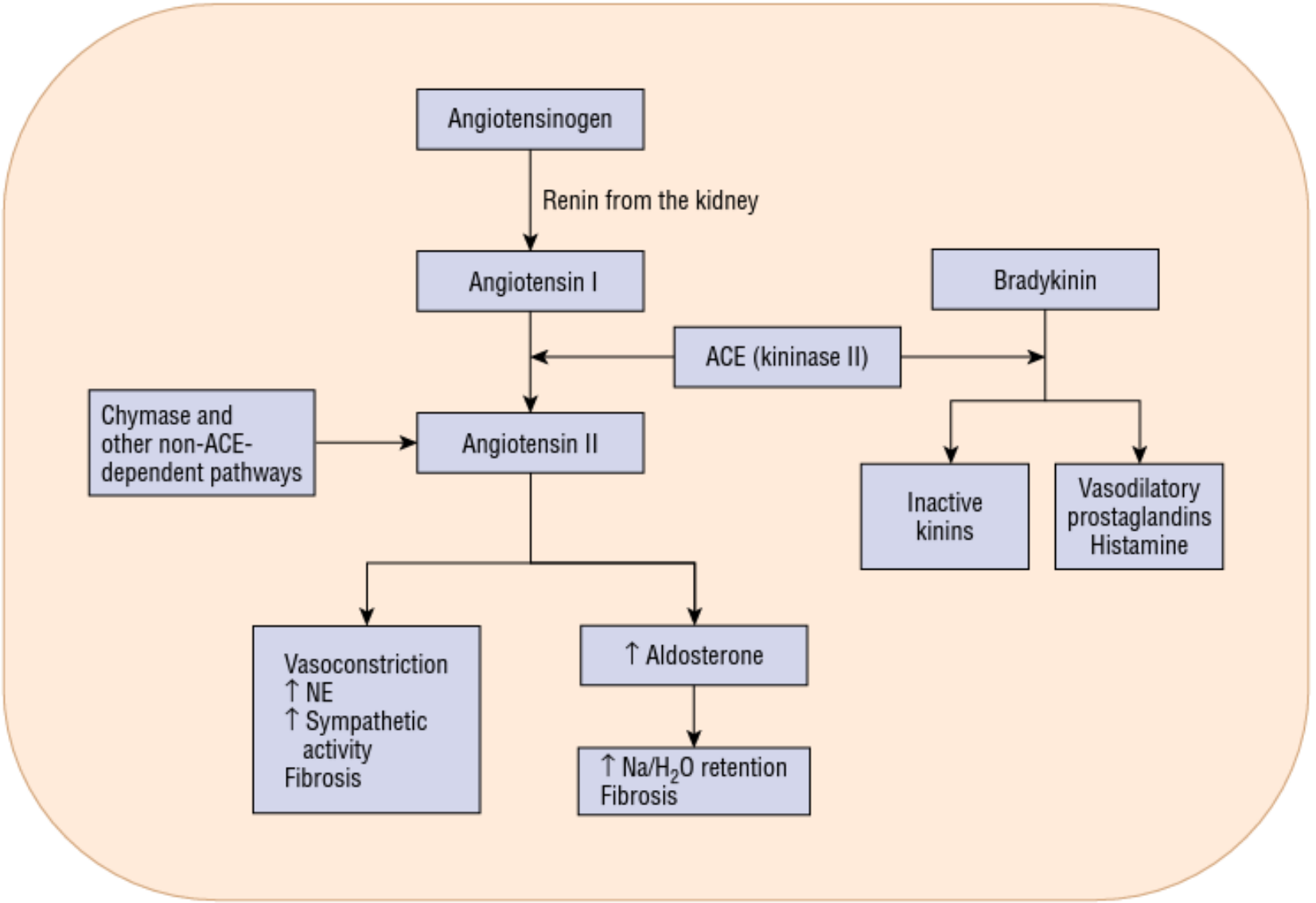


Figure 39-3

Relationship between cardiac output (shown as a cardiac index which is CO/body surface area) and preload (shown as pulmonary artery occlusion pressure).

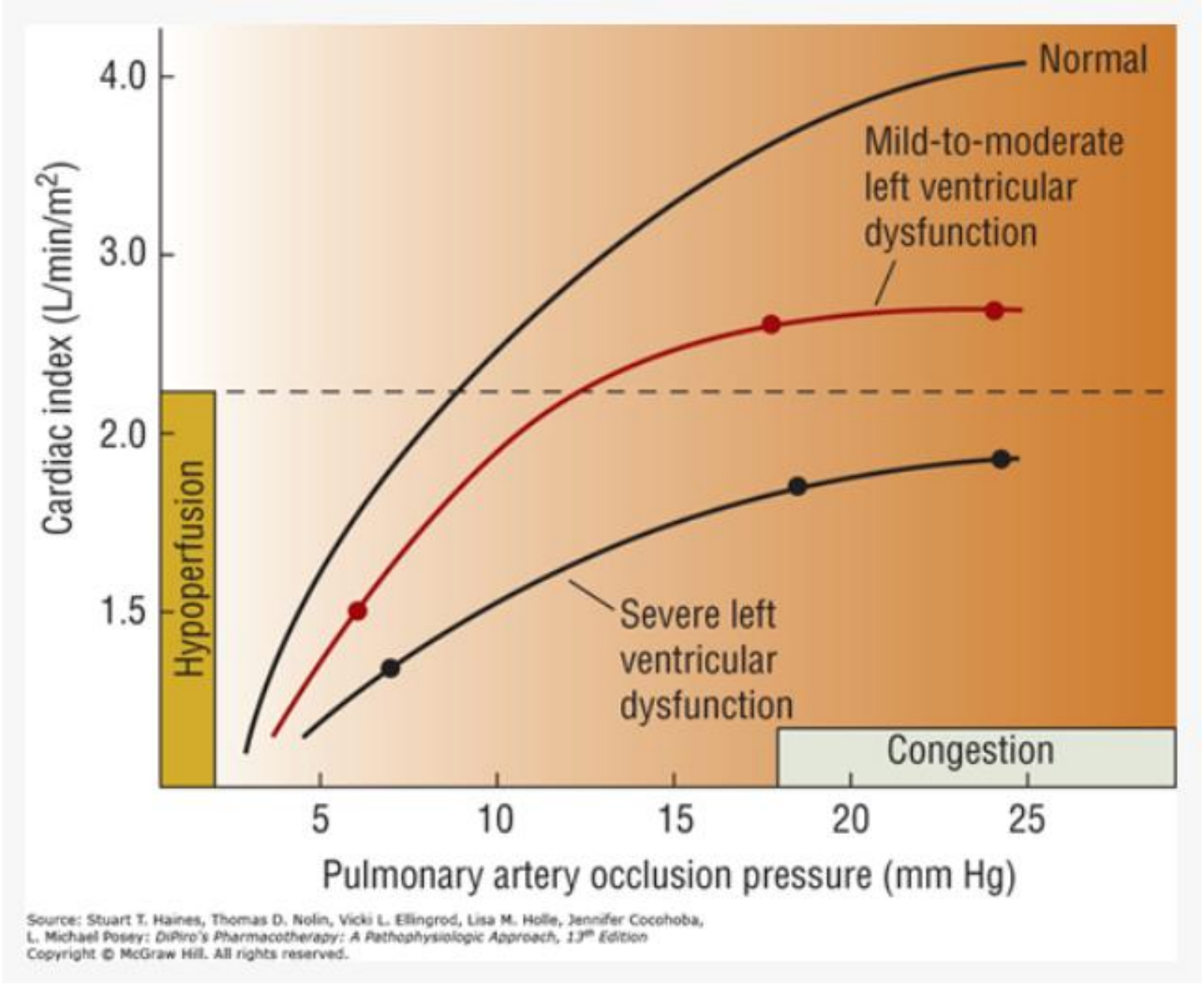
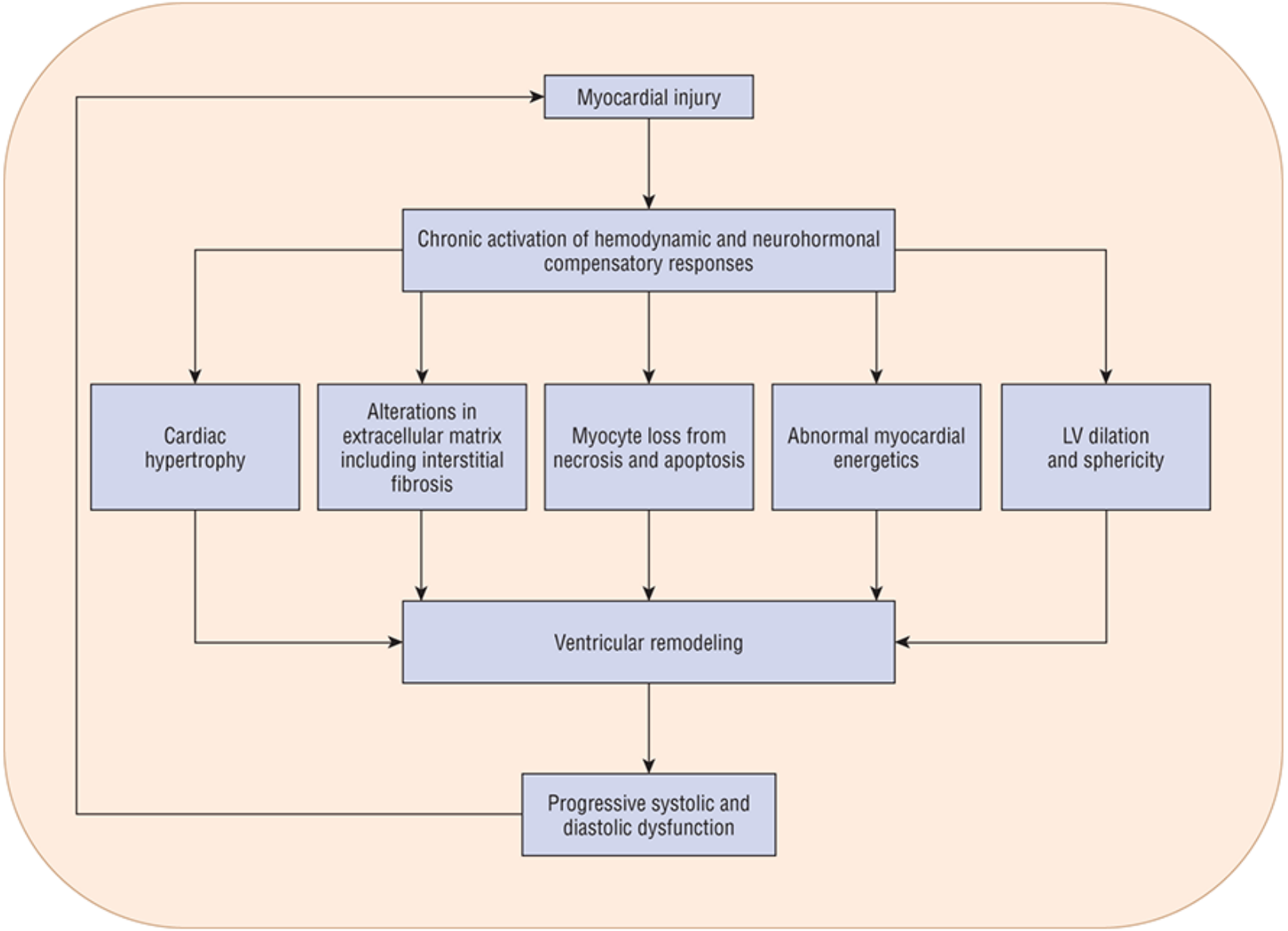


Figure 39-4 Key components of the pathophysiology of cardiac remodeling.

Myocardial injury (eg, MI) results in the activation of a number of hemodynamic and neurohormonal compensatory responses in an attempt to maintain circulatory homeostasis. Chronic activation of the neurohormonal systems results in a cascade of events that affect the myocardium at the molecular and cellular levels. These events lead to th changes in ventricular size, shape, structure, and function known as ventricular remodeling. The alteration in ventricular function result in further deterioration in cardiac systolic and diastolic function that further promote the remodeling.



Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

TABLE 39-3

Beneficial and Detrimental Effects of the Compensatory Responses in Heart Failure

Compensatory Response	Beneficial Effects of Compensation	Detrimental Effects of Compensation
Tachycardia and increased contractility	Increased NE (SNS activation) Helps maintain CO	Shortened diastolic filling time β_1-receptor downregulation, decreased receptor sensitivity Precipitation of ventricular arrhythmias Increased risk of myocardial cell death Increased MVO_2
Vasoconstriction and increased afterload	Increased NE (SNS activation) Increased AT_2 (RAAS activation) Increased BNP Maintains BP despite reduced CO Shunts blood from nonessential organs to brain and heart	Increased afterload decreases SV and further activates the compensatory responses Increased MVO_2
Fluid retention and increased preload	Increased aldosterone (RAAS activation) Increased BNP, AVP, SGLT2 Sodium and water/fluid retention Optimizes SV via Frank-Starling mechanism	Pulmonary and systemic congestion and edema Increased MVO_2
Ventricular hypertrophy and remodeling	Increased NE (SNS activation) Helps maintain CO Reduces myocardial wall stress Decreases MVO_2	Diastolic dysfunction Systolic dysfunction Increased risk of myocardial cell death and ischemia Increased arrhythmia risk Fibrosis

AII, angiotensin II; AVP, arginine vasopressin; BP, blood pressure; CO, cardiac output; MVO_2, myocardial oxygen demand; NE, norepinephrine; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter-2; SNS, sympathetic nervous system.

➢ Factors Precipitating/Exacerbating HF

- ✓ Appropriate therapy can maintain patients in a "compensated" state→ relatively symptom-free
- ✓ Many aggravating or precipitating factors may cause a previously compensated patient to develop worsened symptoms necessitating hospitalization:
- ➢ Cardiac events (MI, atrial fibrillation, uncontrolled HTN)
- ➢ Noncardiac events (pulmonary infections, pulmonary embolus, diabetes, worsening renal function, hypothyroidism, and hyperthyroidism)
- ➢ Nonadherence with prescribed HF medications or with dietary recommendations (eg, sodium intake and fluid restriction)
- ➢ A number of drugs can precipitate or exacerbate HF by one or more of the following mechanisms: (a) negative inotropic effects; (b) direct cardiotoxicity; or (c) increased sodium and/or water retention.

Table 39-4 - Part 1

Selected Drugs That May Precipitate or Exacerbate Heart Failure

Negative Inotropic Effect

Antiarrhythmics (disopyramide, dronedarone, flecainide, propafenone, sotalol)

β-Blockers (eg, propranolol, metoprolol, carvedilol)

Calcium channel blockers—nondihydropyridine type (verapamil, diltiazem)

Itraconazole

Cardiotoxic

Alcohol

Amphetamines (eg, cocaine, methamphetamine)

Antiarrhythmics (proarrhythmic actions—disopyramide, flecainide, propafenone, sotalol)

Cancer Therapies (various)

- Alkylating agents (eg, cyclophosphamide, ifosfamide, melphalan)
- Anthracyclines (eg, doxorubicin, daunorubicin, epirubicin, idarubicin)
- Antimetabolites (eg, fluorouracil, capecitabine, fludarabine, decitabine)
- Antimicrotubules (eg, docetaxel, paclitaxel)
- BCR-ABL inhibitors (eg, bosutinib, dasatinib, imatinib, ponatinib)
- BRAF inhibitors (eg, dabrafenib)
- Hormonal therapy (eg, aplalutamide, bicalutamide, darolutamide, nilutamide)
- Human epidermal growth factor receptor inhibitors (eg, lapatinib, osimertinib)
- Human epidermal growth factor receptor 2 inhibitors (eg, pertuzamab, trastuzumab)
- Immune checkpoint inhibitors (eg, nivolumab, ipilimumab, pembrolizumab)
- Immunomodulators (eg, lenalidomide, pomalidomide, thalidomide)
- MEK inhibitors (eg, binimetinib, cobimetinib, trametinib)
- Mitomycin
- Mitoxantrone
- Vascular endothelial growth factor inhibitors (eg, axitinib. bevacizumab, cabazantinib, lenvatinib, pazopanib, sorafenib, sunitinib, vandetanib)
- Miscellaneous (eg, entrectinib, fedratinib, ripretinib, tretinoin)

Carbamazepine

Table 39-4 - Part 2

Selected Drugs That May Precipitate or Exacerbate Heart Failure

Sodium and Water Retention
Androgens and estrogens
Cyclooxygenase-2 inhibitors
Glucocorticoids
NSAIDs
Pioglitazone and rosiglitazone
Salicylates (high dose)
Sodium-containing drugs (eg, carbenicillin disodium, ticarcillin disodium)
Uncertain Mechanism
Alpha-1 blockers (eg, doxazosin)
Dipeptidyl peptidase-4 inhibitors (eg, saxagliptin, alogliptin)
Gabapentin, pregabalin
Tumor necrosis factor-α inhibitors (eg, adalimumab, infliximab, etanercept)

➢ Clinical presentation

✓ Patient presentation may range from asymptomatic to cardiogenic shock.

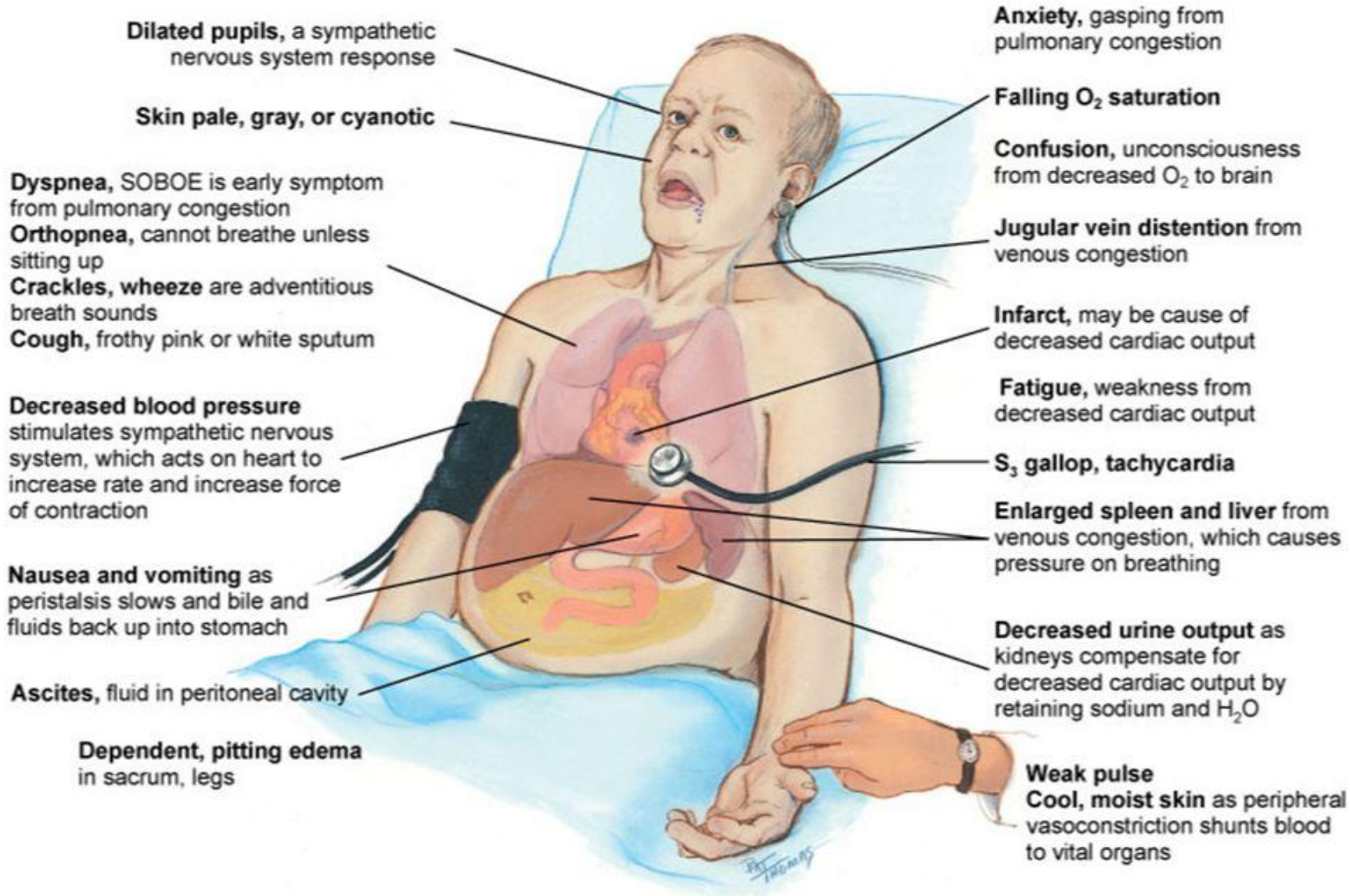
✓ **Symptoms**

Dyspnea, particularly on exertion	Orthopnea	Paroxysmal nocturnal dyspnea
Exercise intolerance	Tachypnea	Cough
Fatigue	Nocturia	Hemoptysis
Abdominal pain	Anorexia	Nausea
Bloating	Ascites	Poor appetite, early satiety
Mental status changes	Weight gain or loss	

✓ **Signs**

Pulmonary rales	Pulmonary edema	S3 gallop	Cool extremities
Pleural effusion	Narrow pulse pressure	Cardiomegaly	Tachycardia
Peripheral edema	Jugular venous distention	Hepatomegaly	

Clinical Portrait of Heart Failure



➢ Laboratory tests

- ✓ B-type natriuretic peptide (BNP)>100 pg/mL and NT-proBNP >300 pg/mL: assist in differentiating dyspnea caused by HF from other causes.
- ✓ Electrocardiogram may be normal or it could show numerous abnormalities including acute changes from myocardial ischemia, atrial fibrillation, bradycardia, left ventricular hypertrophy
- ✓ Serum creatinine: It may be increased due to hypoperfusion. Preexisting renal dysfunction can contribute to volume overload
- ✓ Complete blood count useful to determine if heart failure due to reduced oxygen carrying capacity
- ✓ Chest X-ray: Useful for detection of cardiac enlargement, pulmonary edema, and pleural effusions
- ✓ Echocardiogram: Used to assess LV size, valve function, pericardial effusion, wall motion abnormalities, and ejection fraction
- ✓ Hyponatremia: serum sodium < 130 mEq/L is associated with reduced survival and may indicate worsening volume overload and/or disease progression

➢ Diagnosis

- ✓ HF is often initially suspected in a patient based on symptoms.
- ✓ But, signs and symptoms lack sensitivity for diagnosing HF (they are frequently found with many other disorders).
- ✓ In general, HFpEF cannot be distinguished from HFrEF on the basis of the history, physical examination, chest x-ray, and ECG alone.
- ✓ A complete history and physical examination targeted at identifying cardiac or noncardiac disorders that may cause HF development or progression are essential in the initial patient evaluation.
- ✓ A careful medication history should also be obtained (ethanol, tobacco, NSAIDs).

- ✓ The patient's volume status should be documented by assessing the body weight, JVD, and presence or absence of pulmonary congestion and peripheral edema.

- ✓ Although the history, physical examination, and laboratory tests provide important insight into the underlying cause of HF, the **echocardiogram** is the **single** most useful test in the evaluation of the patient. https://www.youtube.com/watch?v=Kirg2GuESsE

- ✓ The echocardiogram is used to assess abnormalities in cardiac structure and function and should include evaluation of the pericardium, myocardium, and heart valves, and quantification of the LVEF to determine if systolic or diastolic dysfunction is present.

- ✓ Sudden cardiac death, primarily due to ventricular tachycardia and fibrillation, is responsible for 40% to 50% of the mortality in patients with HFrEF.

➢ Treatment of Chronic Heart Failure

✓ Desired Outcomes

The goals of therapy in management of chronic HF are:

1. improve the patient's quality of life
2. relieve or reduce symptoms
3. prevent or minimize hospitalizations
4. slow progression of the disease
5. prolong survival

✓ The ACC/AHA guidelines for the evaluation and management of HF utilize a staging system that not only recognizes the **evolution and progression** of the disorder but also emphasizes **risk factor modification and preventive treatment** strategies (Next Figure).

✓ The general principles used to guide the treatment of HFrEF are based on numerous large, randomized, double-blind, multicenter trials.

✓ With HFpEF (EF is ≥50%) with signs and/or symptoms of HF: Most of the pharmacotherapies known to benefit patients with HFrEF have been less beneficial in HFpEF. Targeting the underlying cause, most commonly uncontrolled HTN, has been the primary strategy for managing patients with HFpEF. However, recent trials have identified treatments that benefit patients with HFpEF as SGLT2 inhibitors, ARBs, spironolactone, & ARNI.

For your reference

Updated figure in the next slide

ACC/AHA Heart Failure Staging System

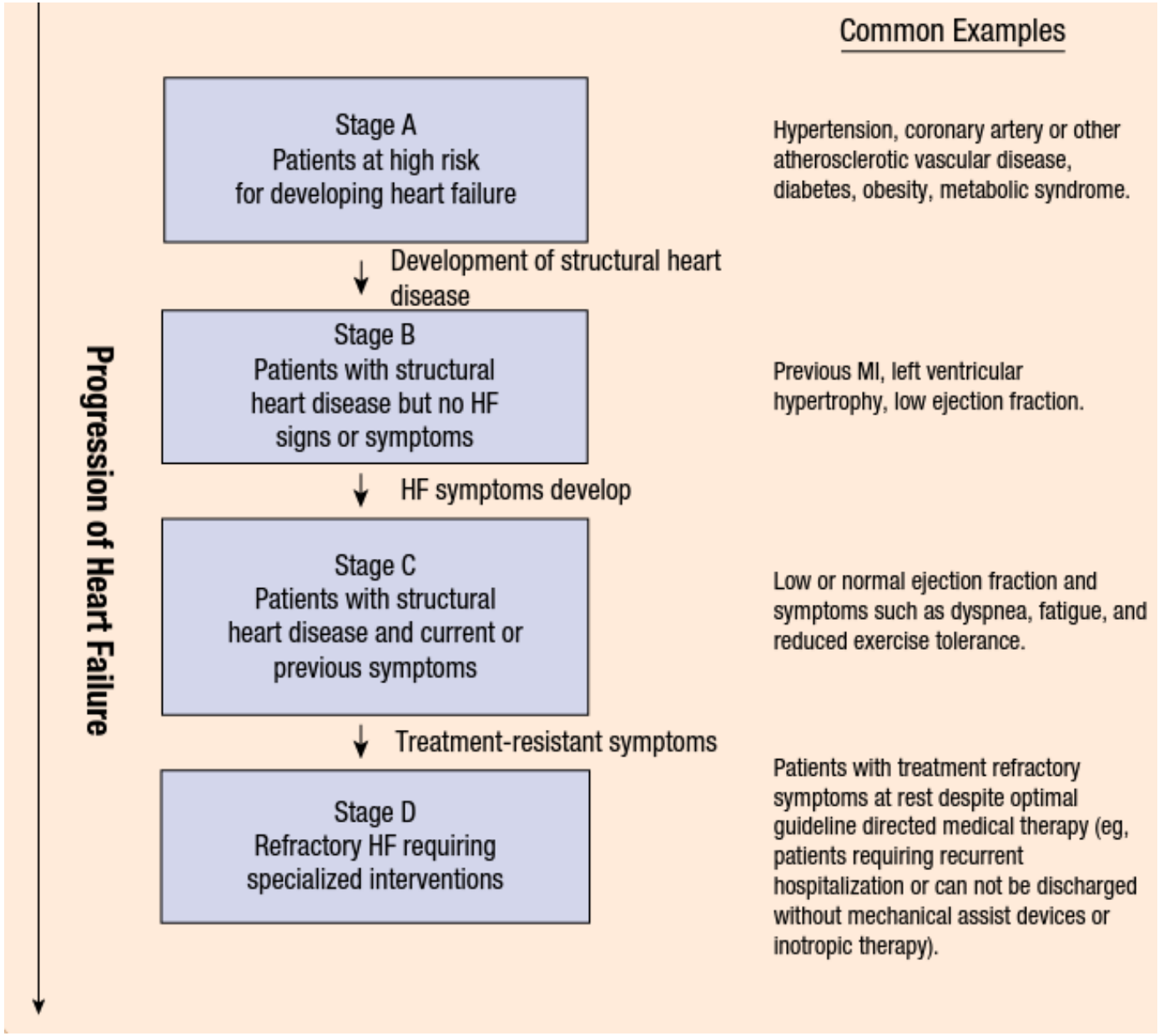
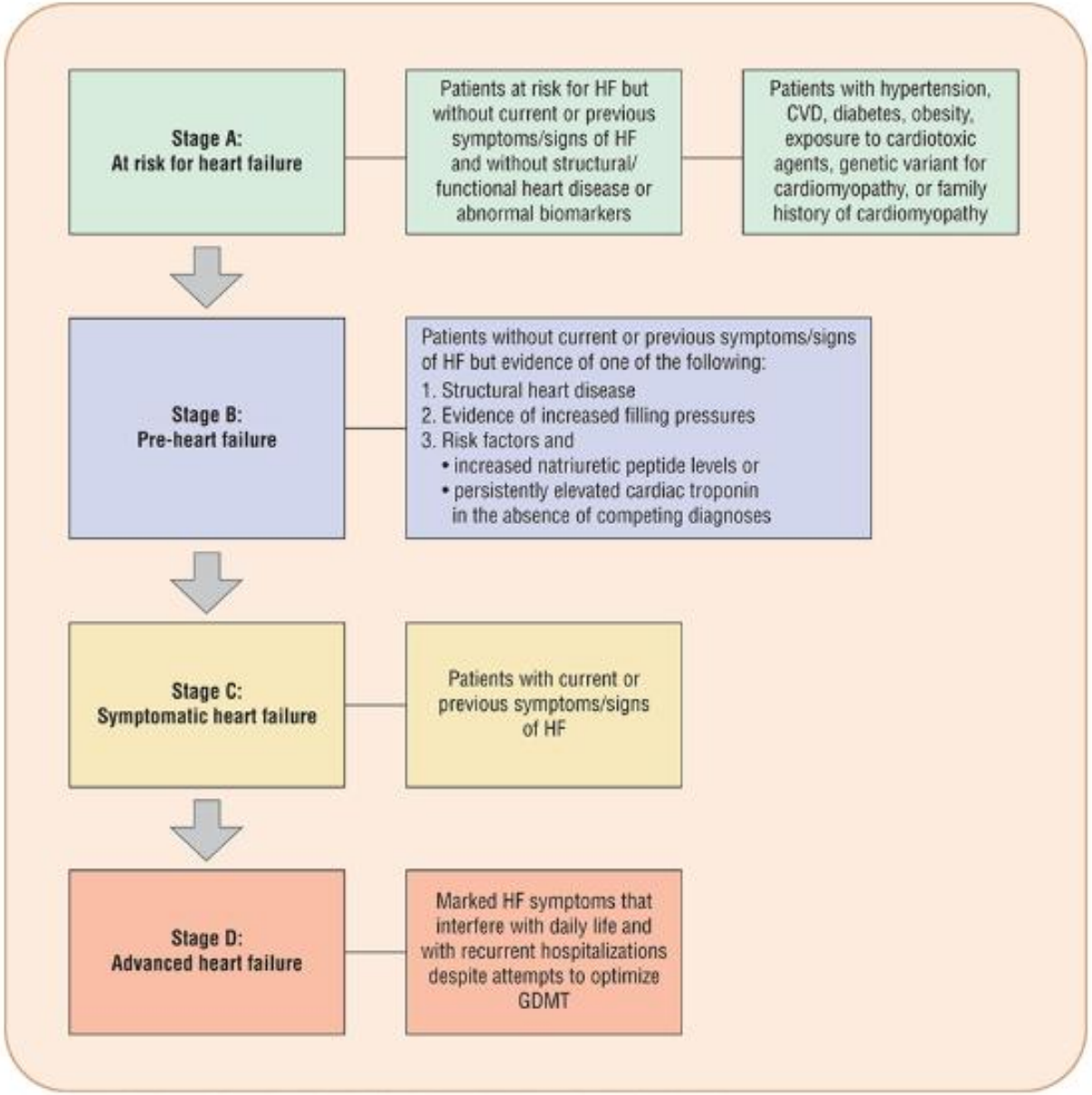


Figure 39-5 Stages of heart failure.

(CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; HF, heart failure.)
(Reprinted, with permission, from Circulation. 2022;145:e876-e894; ©2022 American Heart Association, Inc.)



- ✓ The four stages differ from the NYHA functional classification with which most clinicians are familiar (useful for monitoring patients).
- ✓ The NYHA system is primarily intended to classify symptoms according to the clinician's subjective evaluation and does not recognize preventive measures or the progression of the disorder.
- ✓ A patient's symptoms can change frequently over a short period of time due to changes in medications, diet, intercurrent illnesses, etc.
- ✓ For example, a patient with ACC/AHA Stage C HF with NYHA class IV symptoms such as marked volume overload could rapidly improve to class I to II with aggressive diuretic therapy.
- ✓ In contrast, and consistent with the progressive nature of HF, a patient's ACC/AHA HF stage could not improve (eg, go from Stage C to Stage B) even though the patient's symptoms could fluctuate from NYHA class IV to I.

NEW YORK HEART ASSOCIATION (NYHA) HEART FAILURE CLASSIFICATION

CLASS I

NO LIMITATION OF PHYSICAL ACTIVITY; ORDINARY PHYSICAL ACTIVITY DOES NOT CAUSE SYMPTOMS

CLASS II

SLIGHT LIMITATION OF PHYSICAL ACTIVITY; COMFORTABLE AT REST; ORDINARY PHYSICAL ACTIVITY CAUSES SYMPTOMS

CLASS III

MARKED LIMITATION OF PHYSICAL ACTIVITY; COMFORTABLE AT REST, BUT LESS THAN ORDINARY ACTIVITY CAUSES SYMPTOMS

CLASS IV

SEVERE LIMITATION AND DISCOMFORT WITH ANY PHYSICAL ACTIVITY; SYMPTOMS PRESENT EVEN AT REST

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✓ New York Heart Association Functional Classification Functional class:

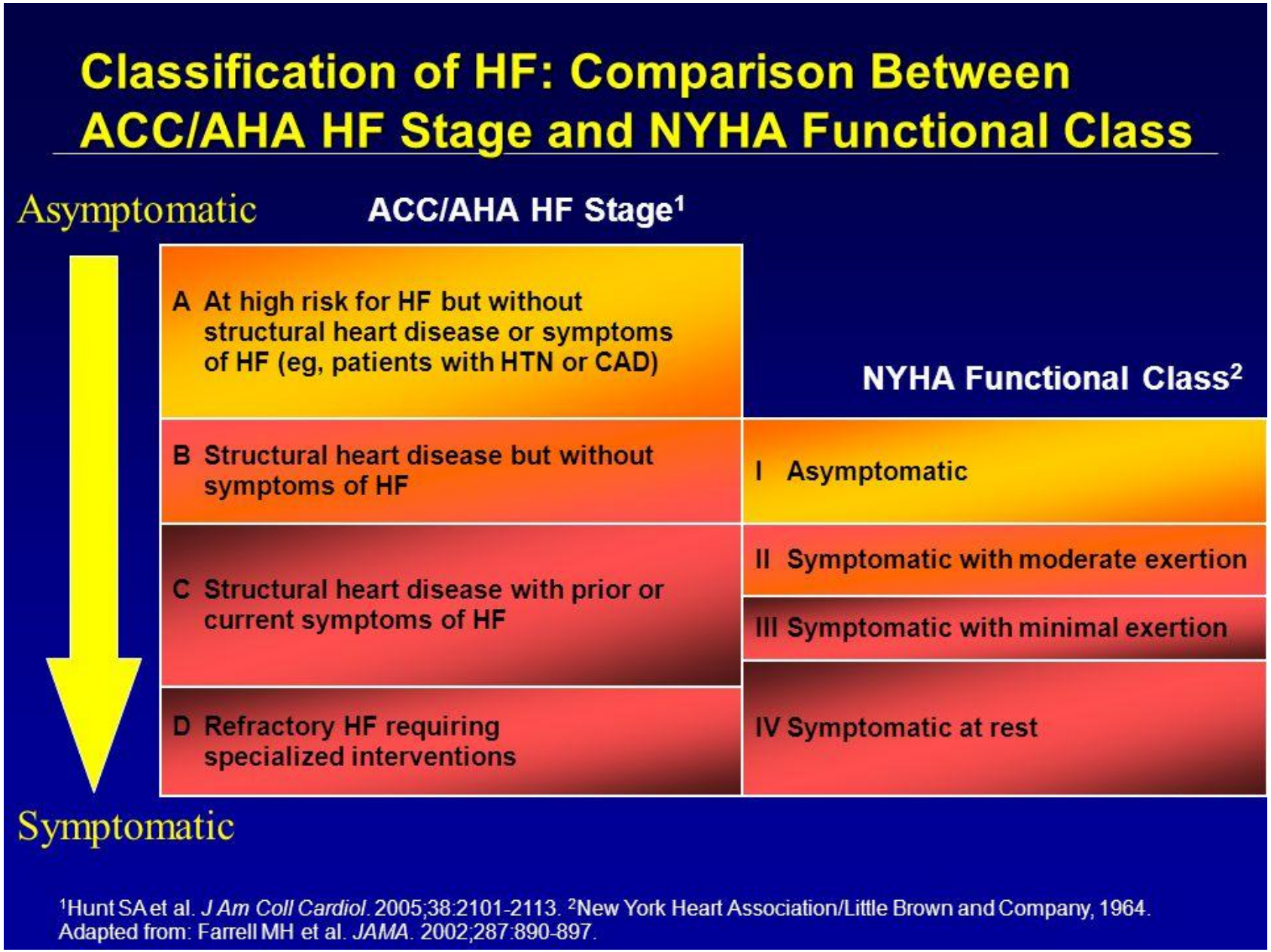
I. Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.

II. Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.

III. Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.

IV. Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

Classification of HF: Comparison Between ACC/AHA HF Stage and NYHA Functional Class



[1]Hunt SA et al. *J Am Coll Cardiol*. 2005;38:2101-2113. [2]New York Heart Association/Little Brown and Company, 1964.
Adapted from: Farrell MH et al. *JAMA*. 2002;287:890-897.

➢ General Measures (including nonpharmacological management)

- ✓ The first step in management of chronic HF is to determine the etiology/precipitating factors.
- ✓ Revascularization or anti-ischemic therapy in patients with CHD may reduce HF symptoms.
- ✓ Drugs that aggravate HF should be discontinued if possible.
- ✓ Restriction of physical activity reduces cardiac workload and is recommended for virtually **all** patients with **acute congestive symptoms**. However, once the patient's symptoms have stabilized and excess fluid is removed, restrictions on physical activity are discouraged.
- ✓ Exercise training may improve functional status and quality of life (supported by current guidelines to improve functional status).

- ✓ Restriction of dietary sodium and fluid intake is an important lifestyle intervention for both HFrEF and HFpEF.
- ✓ Mild (less than 3 g/day) to moderate (less than 2 g/day) sodium restriction, in conjunction with daily measurement of weight, should be implemented to minimize volume retention and allow use of lower and safer diuretic doses.
- ✓ Patients should avoid adding salt to prepared foods and eliminate foods high in sodium (eg, salted snack foods, pickles, and processed foods).
- ✓ In patients with hyponatremia (serum Na less than 130 mEq/L) or those with persistent volume retention despite high diuretic doses and sodium restriction, daily fluid intake should be limited to 2 L/day from all sources.
- ✓ Excessive restriction (Na and fluid) can lead to hypotension, low-output state, and/or renal insufficiency.

- ✓ Dietary and lifestyle factors that decrease the risk of development of CAD and HTN should be encouraged.

- ✓ Other important general measures include patient and family counseling on the signs and symptoms of HF, detailed written instructions on the importance of appropriate medication use and compliance, activity level, diet, discharge medications, weight monitoring, continuity of care, and the need for close monitoring and follow up to reinforce compliance and minimize the risk of HF exacerbations and subsequent hospitalization.

- ✓ These activities are now referred to as **self-care** and constitute an important means to improve such important outcomes as hospitalization and quality of life.

For your reference

Updated figure in the next slide

Treatment algorithm for patients with ACC/AHA Stage A and B heart failure

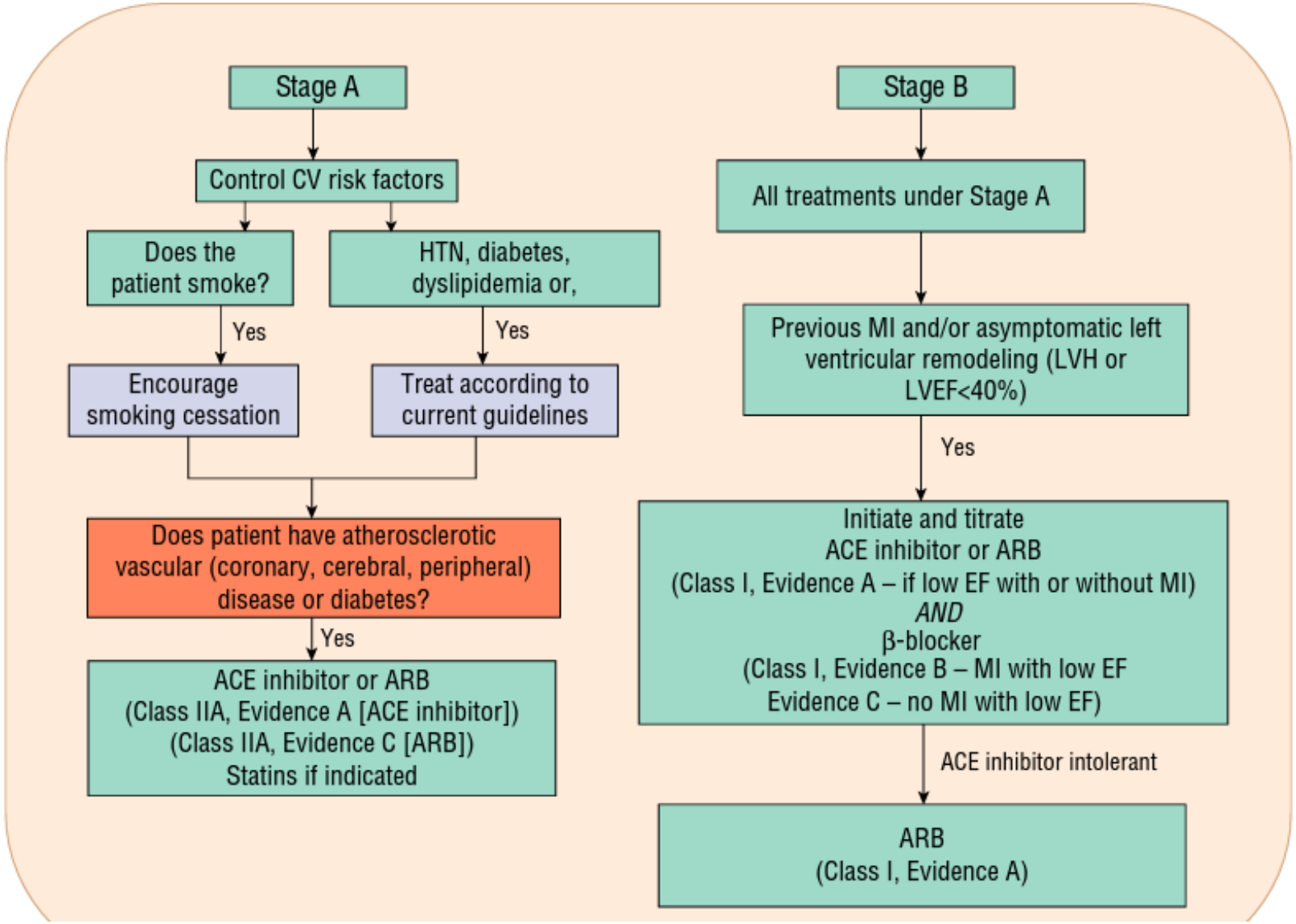
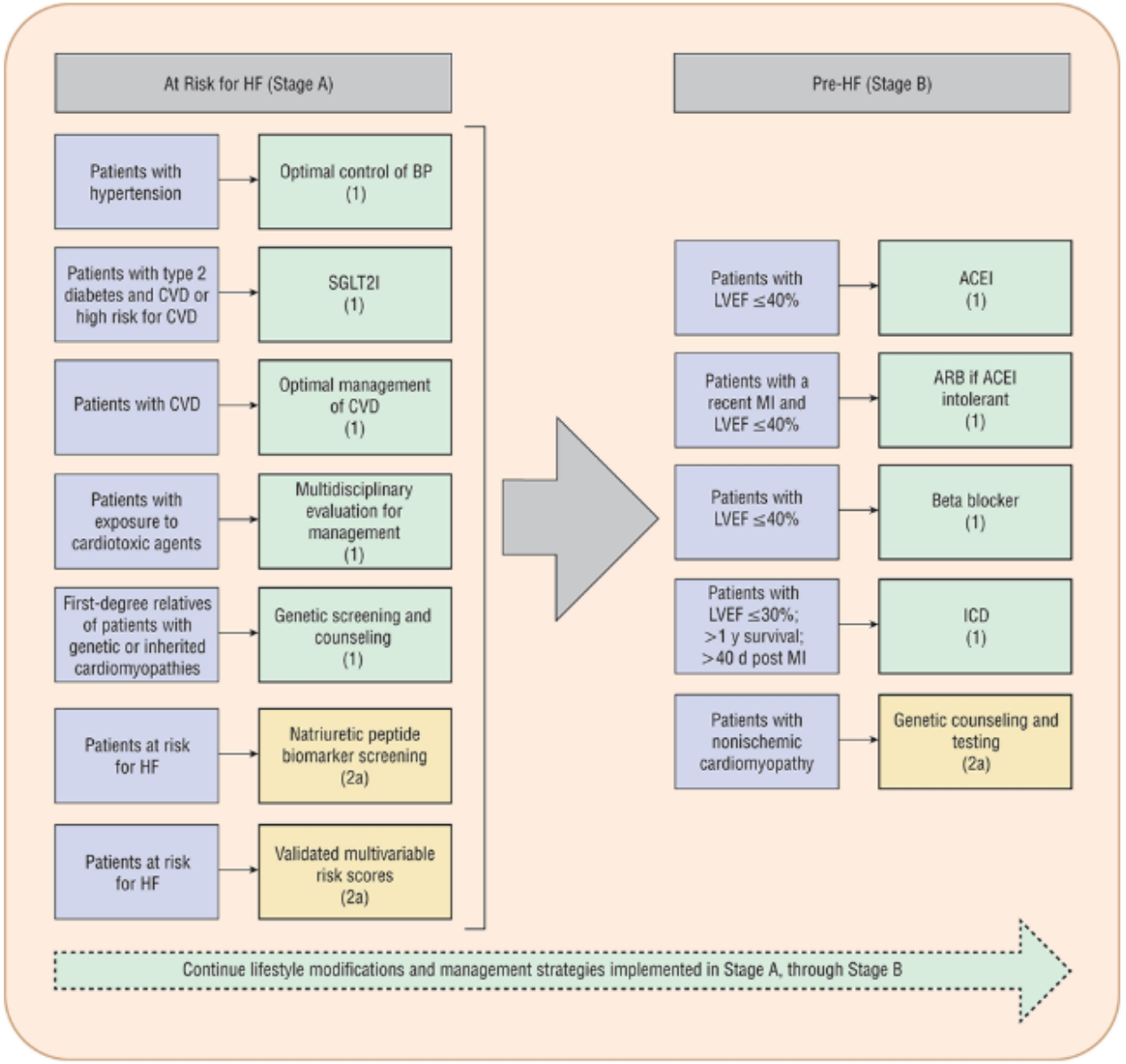


Figure 39-6 Treatment of HFrEF stage A (at Risk for HF) and stage B (pre-HF).

See ACC/AHA/HFSA guidelines for class of recommendation definitions provided under each recommendation (eg, 1, 2a). In brief, **class 1** recommendation refers to conditions for which there is evidence or general agreement that a given procedure/treatment is useful and effective. **Class 2** refers to conditions with conflicting evidence with **2a** having a greater weight/usefulness than **2b**, and **class 3** is for conditions where there is evidence or general agreement that treatment or procedures are not useful/effective or may be harmful. (ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CVD, cardiovascular disease; HF, heart failure; HFSA, Heart Failure Society of America; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SGLT2I, sodium-glucose cotransporter 2 inhibitor.)



➢ Treatment of Stage A Heart Failure:

- ✓ Patients are at high risk for developing HF because of the presence of risk factors.
- ✓ The emphasis here is on risk factor **identification** and **modification** to prevent the development of structural heart disease and subsequent HF.
- ✓ Commonly encountered risk factors include HTN, dyslipidemia, diabetes, obesity, metabolic syndrome, smoking, and coronary artery disease.
- ✓ Effective blood pressure control reduces the risk of developing HF by approximately 50%; thus, current HTN treatment guidelines should be followed.
- ✓ Although treatment must be individualized, ACE inhibitors or ARBs are recommended for HF prevention in patients with **multiple vascular risk factors**. All DM patients should take a SGLT2 inhibitor for HF prevention.

➢ Treatment of Stage B Heart Failure:

- ✓ Patients in Stage B have structural heart disease, but do not have HF symptoms.
- ✓ This group includes patients with left ventricular hypertrophy, recent or remote MI, valvular disease, or LVEF less than 40%. These individuals are at risk for developing HF, and treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process.
- ✓ In addition to the treatment measures outlined in Stage A, SGLT2 inhibitors (if DM present), ACE inhibitors or ARBs and β-blockers are important components of therapy.
- ✓ All patients with a reduced LVEF should receive an ACEI or ARB and a β-blocker to prevent development of HF, whether or not they have had an MI.
- ✓ Patients with a previous MI and reduced LVEF should also receive an ACEI or ARB, evidence-based β-blockers, and a statin.

For your reference

Updated figure in the next slide

Guideline-directed treatment algorithm for patients with ACC/AHA Stage C heart failure with reduced ejection fraction

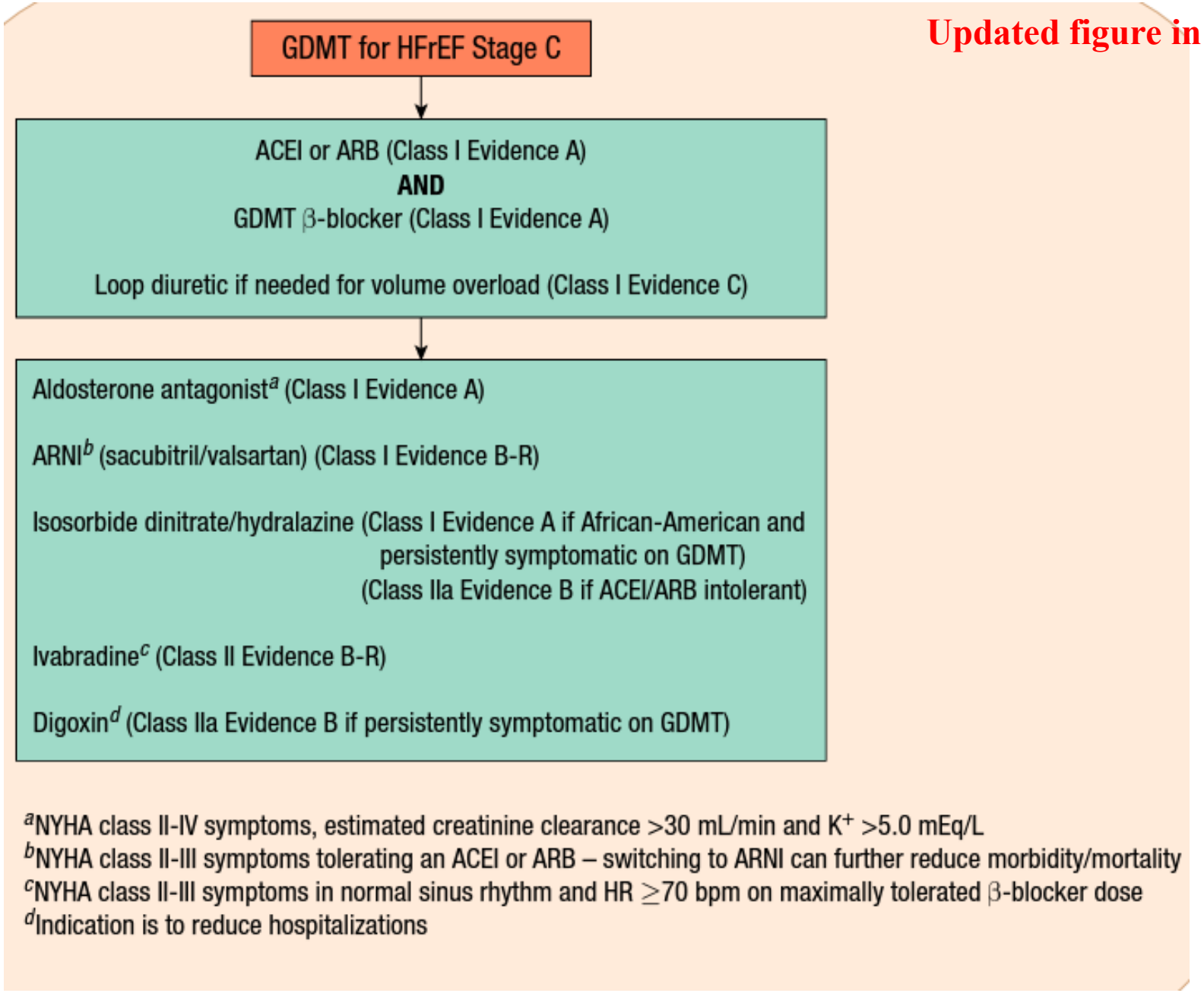
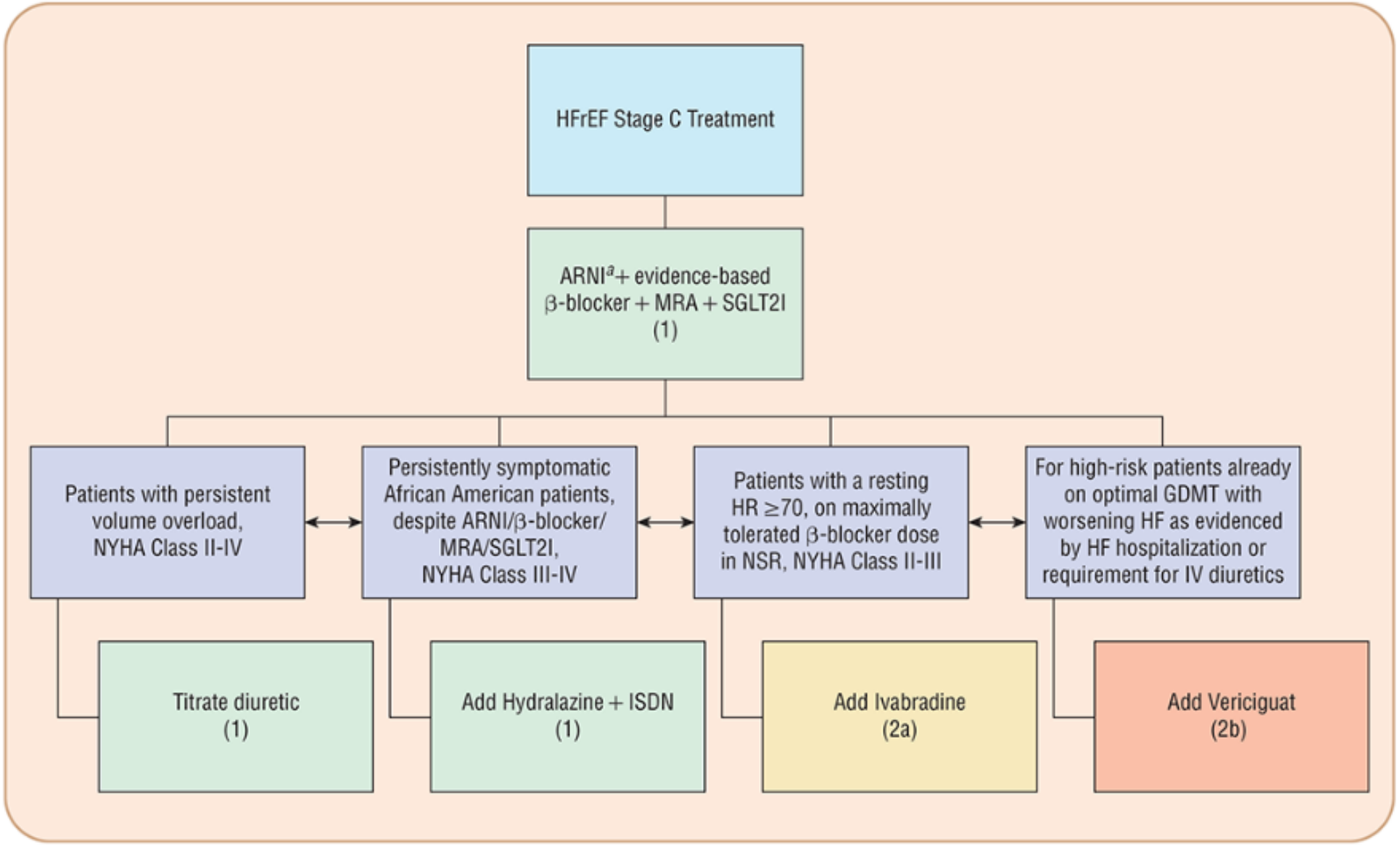


Figure 39-7
Treatment of HFrEF stage C.



Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

Figure 39-7 Treatment of HFrEF stage C.

See ACC/AHA/HFSA for class of recommendation definitions provided under each recommendation (eg, 1, 2a). In brief, **Class 1** recommendation (green) refers to conditions for which there is evidence or general agreement that a given procedure/treatment is useful and effective. **Class 2** refers to conditions with conflicting evidence with **2a** (yellow) having a greater weight/usefulness than **2b** (orange), and **Class 3** is for conditions where there is evidence or general agreement that treatment or procedures are not useful/effective or may be harmful. **a:** ACE inhibitor or ARB should only be used in patients with contraindications, intolerance, or inaccessibility to ARNI. Evidence-based β-blocker refers to metoprolol succinate, bisoprolol, and carvedilol. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker-neprilysin inhibitor; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; ISDN, isosorbide dinitrate MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; and SGLT2I, sodium-glucose cotransporter 2 inhibitor.) (Reproduced with permission from Thomas M. Maddox et al. 2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure with Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. JACC. 2024;83(15);1444-1488.)

➢ Treatment of Stage C HF:

- ✓ Patients with structural heart disease and previous or current symptoms are classified in Stage C and include both HFrEF and HFpEF.
- ✓ Patients should be routinely treated with guideline directed medical therapy (GDMT) that includes an ARNI (sacubitril/valsartan), ACEI or ARB, an evidence-based β-blocker, SGLT2 inhibitor, MRA, and diuretic therapy.
- ✓ The benefits of these medications on slowing HF progression, reducing morbidity and mortality, and improving symptoms are clearly established.
- ✓ Hydralazine-ISDN can also be used in these patients.
- ✓ Digoxin can also be considered in selected patients (to decrease hospitalizations in patients with HFrEF that remain symptomatic despite GDMT or added during initial treatment of patients with severe symptoms while GDMT is started), as can newly approved medications, ivabradine & others.

- ✓ Nonpharmacologic therapy with devices such as an implantable cardioverter-defibrillator (ICD) is also indicated in certain patients with HFrEF in Stage C.

- ✓ Other general measures noted earlier are also important as is careful follow up and patient education to reinforce dietary and medication compliance to prevent clinical deterioration and reduce hospitalization.

- ➢ **Treatment of Stage D HFrEF:**

- ✓ Stage D HF includes patients receiving maximally tolerated GDMT that have persistent symptoms.

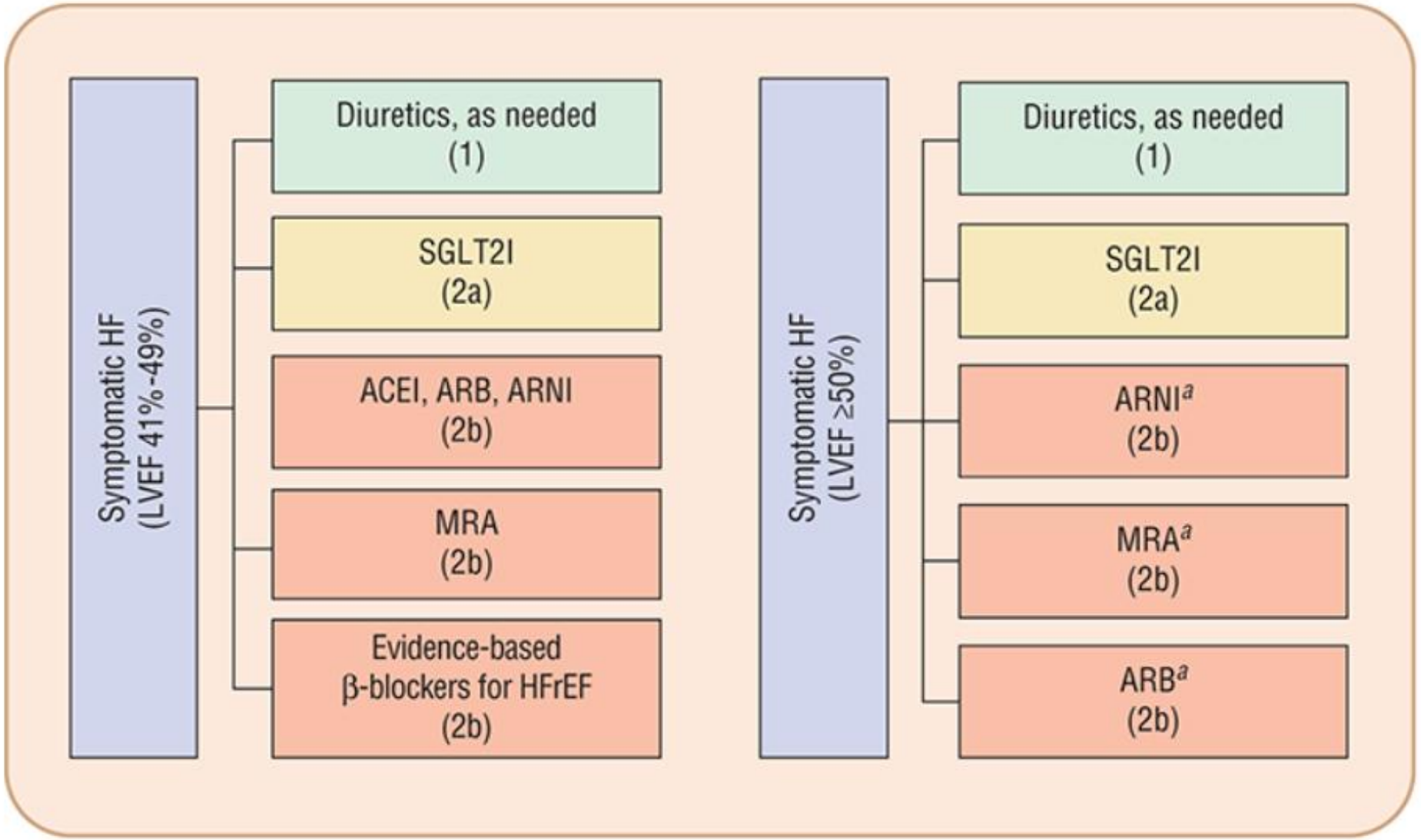
- ✓ This is often referred to as advanced, refractory, or end-stage HF.

- ✓ These patients often undergo recurrent hospitalizations or cannot be discharged from the hospital without special interventions, have a poor quality of life, and are at high risk for morbidity and mortality.

- ✓ These individuals have the most advanced form of HF and specialized therapies including mechanical circulatory support, continuous IV positive inotropic therapy, and cardiac transplantation can be considered in addition to standard treatments outlined in Stages A to C.

- ✓ Discussions with the patient and family members regarding prognosis, patient priorities for minimizing symptoms versus prolonging survival and end-of-life and hospice care should be initiated.

Figure 39-8
Treatment of HFmrEF and HFpEF.



Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

Figure 39-8 Treatment of HFmrEF and HFpEF.

See ACC/AHA/HFSA guidelines for class of recommendation definitions provided under each recommendation (eg, 1, 2a). In brief, **class 1** recommendation refers to conditions for which there is evidence or general agreement that a given procedure/treatment is useful and effective. **Class 2** refers to conditions with conflicting evidence with **2a** having a greater weight/usefulness than **2b**, and **class 3** is for conditions where there is evidence or general agreement that treatment or procedures are not useful/effective or may be harmful. aGreater benefit in patients with an LVEF closer to 50% (0.5). Evidence-based β-blocker refers to metoprolol succinate, bisoprolol, and carvedilol. (ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2I, sodium-glucose cotransporter 2 inhibitor.)

TABLE. Recommendations for Use of SGLT2 inhibitors in HF[1]

Stage of HF	Recommendation	COR
Stage A, at risk for HF	To prevent HF hospitalization in patients with T2D who have CVD or are at high risk for CVD	1
Stage C, symptomatic HF		
HFrEF	To reduce HF hospitalization and CV mortality in patients with symptomatic chronic HFrEF, regardless of the presence of T2D	1
HFpEF	To reduce HF hospitalizations and CV mortality in patients with HFpEF	2a
HFmrEF	To reduce HF hospitalizations and CV mortality in patients with HFmrEF	2a

COR, class of recommendation; CVD, cardiovascular disease; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes

For your reference

ACC/AHA/HFSA 2022 Update

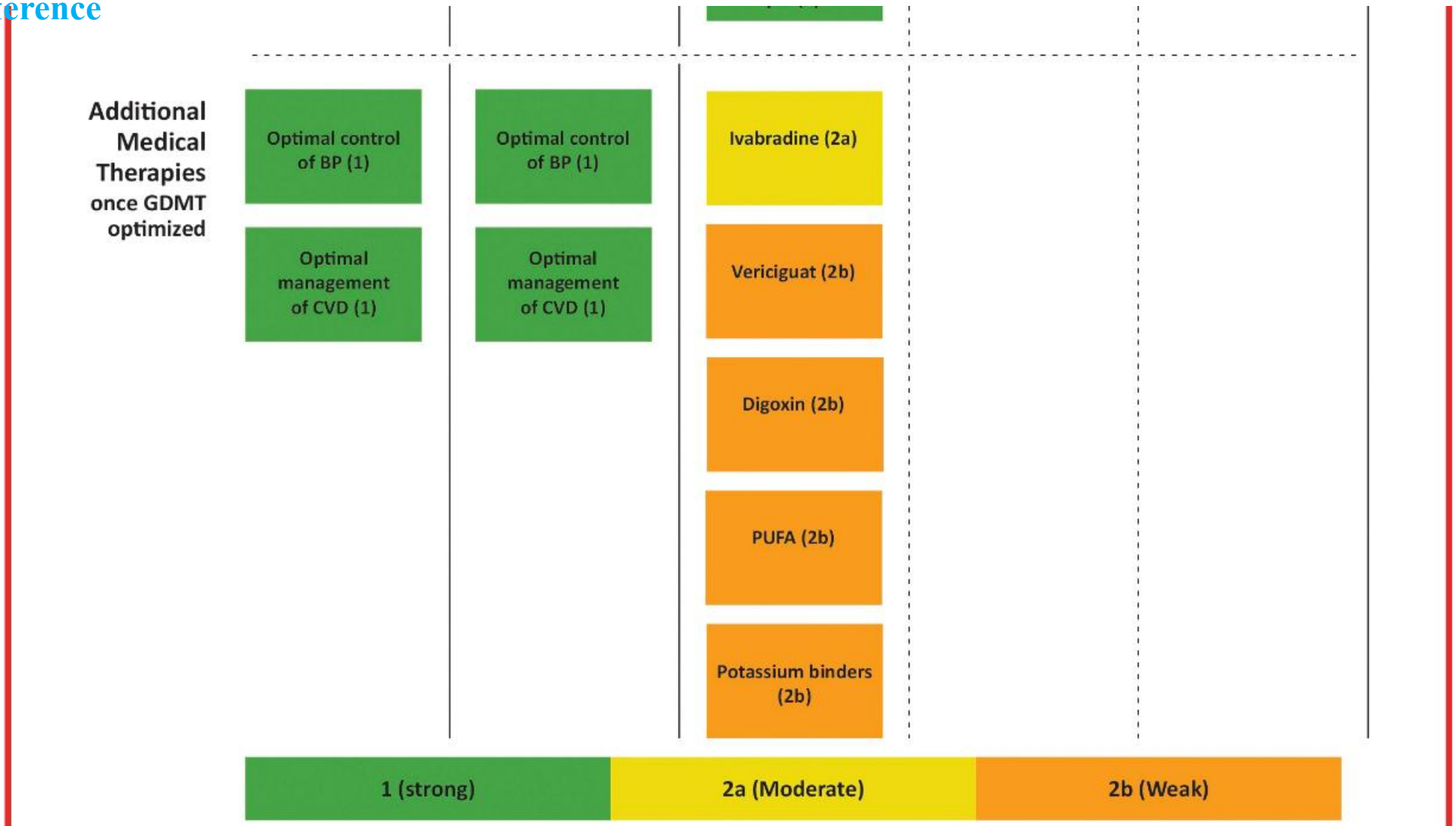
CENTRAL ILLUSTRATION: 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Guideline Directed Medical Therapy Across Heart Failure Stages

Use this tool to reference guideline directed medical therapy (GDMT) across the four ACC/AHA stages of Heart Failure (HF) as outlined in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. See the guideline for specific patient population criteria.

GDMT of major medication classes	Stage A At-Risk for Heart Failure	Stage B Pre-Heart Failure	Stage C & D Stage C: Symptomatic Heart Failure & Stage D: Advanced Heart Failure HFrEF LVEF ≤40%	HFmrEF LVEF 41-49%	HFpEF LVEF ≥50%
	SGLT2i in pts with DM (1)	SGLT2i in pts with DM (1)	ARNI in NYHA II-III; ACEi or ARB in NYHA II-IV (1)	Diuretics, as needed (1)	Diuretics, as needed (1)
		ACEi (1)	Beta blocker (1)	SGLT2i (2a)	SGLT2i (2a)
		ARB if ACEi intolerant (1)	MRA (1)	ACEi, ARB, ARNi (2b)	ARNi (2b)
		Beta blocker (1)	SGLT2i (1)	MRA (2b)	MRA (2b)
			Diuretics, as needed (1)	Beta blocker (2b)	ARB (2b)
			Hydral-nitrates for NYHA III-IV, in African American pts (1)		

For your reference



Heidenreich PA, et al. J Am Coll Cardiol. 10.1016/j.jacc.2021.12.012

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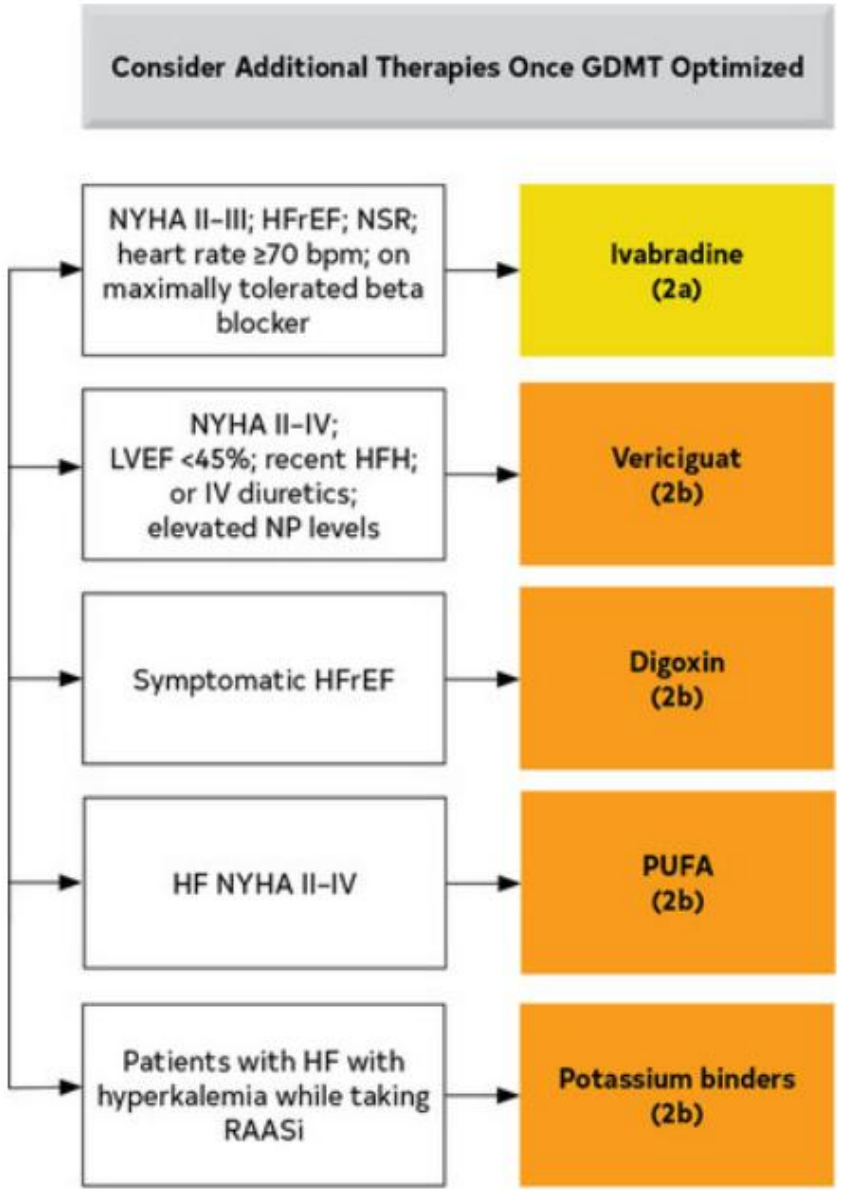


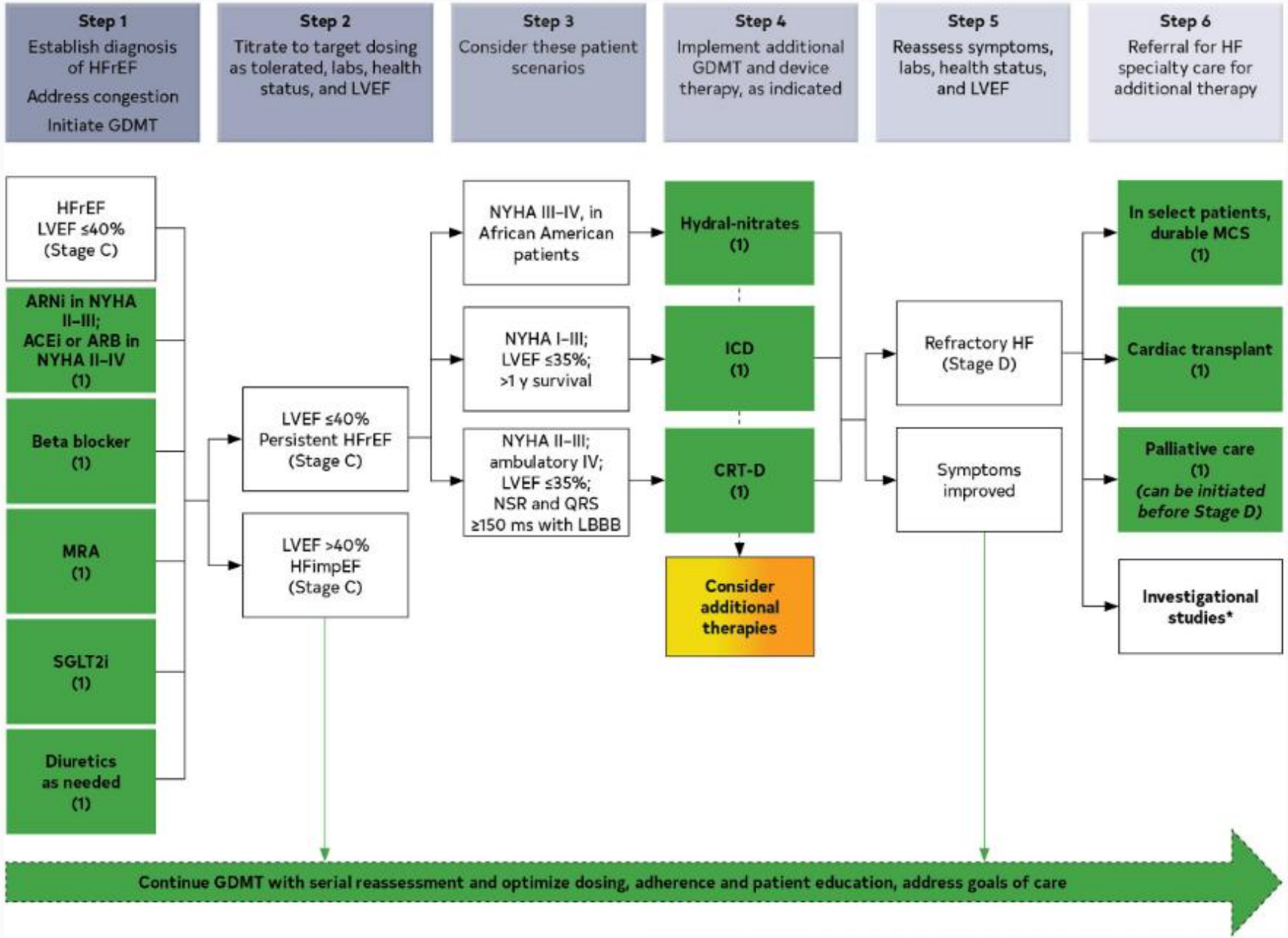
Oral soluble guanylyl cyclase stimulator directly binds and stimulates sGC and increases cGMP production (vasodilation, improvement in endothelial function, decrease in fibrosis and remodeling of the heart).

Omega-3 polyunsaturated fatty acids

Patiromer and sodium zirconium cyclosilicate (SZC) - remove potassium by exchanging cations

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

For your reference



Treatment of HFrEF Stages C and D. Colors correspond to COR in Table 2. Treatment recommendations for patients with HFrEF are displayed. Step 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF. Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication. Medication doses should be increased to target as tolerated. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; COR, Class of Recommendation; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; MCS, mechanical circulatory support; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; and SGLT2i, sodium-glucose cotransporter 2 inhibitor. *Participation in investigational studies is appropriate for stage C, NYHA class II and III HF.

Table 39-8 Cardiovascular and Noncardiovascular Comorbidities – Part 1

CV Comorbidity	Recommendations and Comments
Hypertension	• Treat according to ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults • Target BP <130/80 mm Hg, unless evidence for symptomatic hypotension, labile BP, or observed impact on kidney dysfunction • Preferred therapies: diuretic agent, ARNI, ARB, MRA • In HFrEF, addition of hydralazine/ISDN or a dihydropyridine CCB (amlodipine, felodipine) may be considered • Both verapamil and diltiazem should be avoided in HFrEF but can be safely used in HFpEF; however, use caution with aggressive HR lowering
Dyslipidemia	Treat according to current AHA/ACC/Multi-society guideline on the management of blood cholesterol and the ACC ECDP on the role of nonstatin therapies for LDL-cholesterol lowering in the management of ASCVD risk
Coronary artery disease	• Treat according to current ACC/AHA/SCAI guideline for coronary artery revascularization and the ACC/AHA/ASE/CHEST/SAEM/SCCT/SCMR guideline for evaluation and diagnosis of chest pain • Surgical revascularization in appropriate patients • β-Blockers and nitrates are preferred antianginals for patients with both HFrEF and CAD • Amlodipine and felodipine are safe in HFrEF, while nondihydropyridines and CCBs (verapamil, diltiazem) should be avoided • β-Blockers and verapamil are safe and have neutral effects on outcomes in HFpEF; however, use caution with aggressive HR lowering given low SV at rest and poor SV reserve during exertion • In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective, and long-acting nitrates appear to hinder activity level • Optimize therapies for secondary prevention of coronary and atherosclerotic vascular disease
Atrial fibrillation	• Treat according to the current ACC/AHA/ACCP/HRS guideline for the management of patients with AF • Anticoagulation as indicated • Rate vs rhythm control guided by HF symptoms • AF ablation recommended, if symptoms attributable to AF and HFrEF or HFpEF (*less evidence in HFpEF*) • AV node ablation with CRT implantation recommended, if LVEF ≤50% (0.5) and rhythm control strategies fail or are undesirable (*less evidence*) • In HFrEF, β-blockers are more effective for rate control than digoxin and improve morbidity and mortality. Combination of β-blockers and digoxin may be more effective at rate control. Nondihydropyridine CCBs (verapamil, diltiazem) should be avoided • In HFpEF, β-blockers and nondihydropyridine CCBs are often considered first-line agents for HR control; however, as described above, aggressive rate control should be avoided • Exercise caution when treating with digoxin • In HFrEF, amiodarone and dofetilide are preferred for rhythm control, and avoid class I antiarrhythmics and dronedarone

Table 39-8 Cardiovascular and Noncardiovascular Comorbidities – Part 2

Non-CV Comorbidity	Recommendations and Comments
Diabetes	• Treat according to the current ACC ECDP on novel therapies for CV risk reduction in patients with T2DM and ADA standards of medical care in diabetes • Consider consulting with endocrinologist • SGLT2 inhibitors as first-line therapies for comorbid T2DM and HF regardless of EF • GLP-1 receptor agonists are an option in individuals with high CV risk and/or obesity • Finerenone in diabetic kidney disease • Avoid thiazolidinediones and DDP-4 inhibitors (saxagliptin, alogliptin)
Chronic kidney disease	• Treat according to KDIGO clinical practice guidelines for the evaluation and management of CKD and guideline for diabetes management in CKD • Optimize RAAS inhibitor therapy • Use hydralazine/ISDN if an ARNI/ACE inhibitor/ARB cannot be used • Treat with SGLT2 inhibitor if GFR allows • Consider potassium binders for hyperkalemia • Consider nephrology consult

ACC, American College of Cardiology; ACCP, American College of Clinical Pharmacy; ACE, angiotensin-converting enzyme; ADA, American Diabetes Association; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; ASE, American Society of Echocardiography; AV, atrioventricular; BP, blood pressure; CCB, calcium channel blockers; CHEST, American College of Chest Physicians; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; CV, cardiovascular; DDP-4, dipeptidyl peptidase-4; ECDP, Expert Consensus Decision Pathway; GDMT, guideline-directed medical therapy; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HRS, Heart Rhythm Society; ISDN, isosorbide dinitrate; KDIGO, Kidney Disease Improving Global Outcomes; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; QOR, quality of life; RAAS, renin-angiotensin-aldosterone system; SAEM, Society for Academic Emergency Medicine; SCAI, Society for Cardiovascular Angiography & Interventions; SCCT, Society for Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance; SGLT2, sodium-glucose cotransporter-2; T2DM, type 2 diabetes mellitus.

Table 39-9 Specific Patient Subpopulations

Subpopulation	Recommendations and Comments
Pregnancy	• Multidisciplinary management and GDMT with reasonable safety profile • Pregnancy contraindicated for women with LVEF <30% (0.3) (NYHA class III/IV) or history of PPCM with LVEF <50% (0.5) (WHO class IV) • Baseline and monitor BNP/NT-proBNP • ACE inhibitors, ARB, ARNI, and MRA are contraindicated in pregnancy • Avoid hypotension and over-diuresis • Preferred HF agents: β-blockers, diuretics, ISDN, hydralazine • Following delivery, if breastfeeding then assess drug distribution of current HF therapies into breast milk
Patients with cancer	• Requires multidisciplinary management and treatment plan will vary based on the type of cancer, the cancer therapy used, and other factors specific to the patient • ARB, ACE inhibitor, and β-blocker GDMT for select asymptomatic patients with cancer therapy–related cardiomyopathy (LVEF <50% [0.5])
African American patients, self-identified	• GDMT • Angioedema risk possibly higher with ACE inhibitors and ARBs compared to White patients • Angioedema risk with ARNIs may not be different from White patients
Patients living with frailty per established criteria	• GDMT as tolerated • Uncertain response to GDMT, treat as tolerated • Possible increased risk of adverse drug reactions
Adults ≥75 years	• GDMT but recognize that this population is excluded from many trials supporting GDMT • Consider starting with lower doses of GDMT • Common potential risks: falls, worsening of kidney function, polypharmacy, comorbidity, depression, financial toxicity

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; GDMT, guideline-directed medical therapy; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; (NT-pro)BNP, (aminoterminal-prohormone) B-type natriuretic peptide; NYHA, New York Heart Association; PPCM, peripartum cardiomyopathy; WHO, World Health Organization

Drug Dosing Table

Drug	Initial Dose	Usual Range	Special Population	PK/PD Considerations, Key Drug Interactions, Other Concerns
Loop Diuretics				When used in combination with thiazide diuretics, there is an additive risk of hypokalemia, hypomagnesemia, and volume depletion with related renal dysfunction.
Furosemide	**20-40 mg once or twice daily**	**20-160 mg once or twice daily**	Clcr 20-50 mL/min: 160 mg once or twice daily Clcr<20 mL/min: 400 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
Bumetanide	0.5-1.0 mg once or twice daily	1-2 mg once or twice daily	ClCr 20-50 mL/min: 2 mg once or twice daily Clcr<20 mL/min: 8-10 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
Torsemide	10-20 mg once daily	10-80 mg once daily	ClCr 20-50 mL/min: 40 mg once daily Clcr<20 mL/min: 200 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
Guideline-Directed Medical Therapy for HFrEF and HFpEF				
1) ACEIs:				All ACEIs: Additive risk of hyperkalemia with other medications that increase serum potassium (eg, potassium supplements). Additive risk of renal dysfunction with diuretics, NSAIDs, and other nephrotoxins
Captopril	**6.25 mg three times daily**	**50 mg three times daily***		

Drug	Initial Dose	Usual Range	PK/PD Considerations, Key Drug Interactions, Other Concerns
Enalapril	**2.5 mg twice daily**	**10-20 mg twice daily***	
Lisinopril	2.5-5.0 mg once daily	20-40 mg once daily*	
Ramipril	1.25-2.5 mg	5 mg twice daily*	
Fosinopril	5-10 mg once daily	40 mg once daily	Undergoes both hepatic and renal elimination
1) ARBs:			All ARBs: Additive risk of hyperkalemia with other medications that increase serum potassium (eg, potassium supplements). Additive risk of renal dysfunction with diuretics, NSAIDs, and other nephrotoxins
Candesartan	**4 mg once daily**	**32 mg once daily***	Candesartan is a prodrug
Valsartan	20-40 mg twice daily	160 mg twice daily*	
Losartan	25-50 mg once daily	150 mg once daily*	Prodrug
1) Angiotensin Receptor Blocker/Neprilysin Inhibitor:			
Sacubitril/ Valsartan (Entresto)	49/51 mg twice daily 24/26 mg twice daily if not taking or low dose of ACE inhibitor/ARB or if eGFR is <30 mL/min/1.73 m2	97/103 mg twice daily *	Discontinue ACE inhibitors at least 36 hours prior to initiation Additive risk of hyperkalemia with other medications that increase serum potassium (eg, potassium supplements) Additive risk of renal dysfunction with diuretics, NSAIDs, and other nephrotoxins

Drug	Initial Dose	Usual Range	Special Population	PK/PD, Key Drug Interactions, Other Concerns
2) β-blockers:				
Bisoprolol	1.25 mg once daily	10 mg once daily*		
Carvedilol	**3.125 mg twice daily**	**25 mg twice daily***	**Target dose for patients weighing >85 kg is 50 mg twice daily**	Should be taken with food
Carvedilol phosphate	10 mg once daily	80 mg once daily		Should be taken with food
Metoprolol succinate CR/XL	**12.5-25 mg once daily**	**200 mg once daily***		
3) MRAs: Aldosterone Antagonists				- If eGFR 30-49 mL/min/1.73 m2: reduce dose or frequency - Risk of hyperkalemia increases if serum creatinine >1.6 mg/dL (141 µmol/L). Avoid if baseline potassium is >5 mEq/L (mmol/L) - Additive risk of hyperkalemia with other medications that increase serum potassium (eg, ACE inhibitors, ARBs, ARNIs, potassium supplements)
Spironolactone	eGFR ≥50 mL/min /1.73m^2: **12.5-25 mg once daily**	**25-50 mg once daily***	eGFR 30-49 mL/min/1.73m^2: 12.5 mg once daily or every other day	
Eplerenone	eGFR ≥50 mL/min /1.73m^2: 25 mg once daily	50 mg once daily*	eGFR 30-49 mL/min/1.73m^2: 25 mg every other day	Eplerenone is a substrate of CYP3A4
Finerenone (Kerendia)	10 mg once daily	20 mg once daily		Finerenone is currently only FDA-approved for chronic kidney disease with type 2 diabetes

Drug	Initial Dose	Usual Range	PK/PD Considerations, Key Drug Interactions, Other Concerns
4) SGLT2 Inhibitors:			Increased risk of ketoacidosis and volume depletion in patients with diabetes
Dapagliflozin (Farxiga)	10 mg once daily	10 mg once daily	Dapagliflozin should not be initiated if eGFR ≤25 mL/min/1.73 m2
Empagliflozin (Jardiance)	**10 mg** **once daily**	**10 mg** **once daily***	
Sotagliflozin (Inpefa)	200 mg once daily	400 mg once daily	Sotagliflozin should not be initiated if eGFR ≤25 mL/min/1.73 m2 Sotagliflozin may increase digoxin exposure

Drug	Initial Dose	Usual Range	PK/PD Considerations, Key Drug Interactions, Other Concerns
Additional therapies for HFrEF or HFpEF or other cardiomyopathies			
Hydralazine-Isosorbide Dinitrate (Bidil) (fixed-dose combination) -or- Individual agents not in fixed-dose combination	Fixed-dose combination: 37.5-mg hydralazine plus 20-mg isosorbide three times daily Individual agents: 25-50 mg hydralazine plus 20-30 mg isosorbide dinitrate 3-4 times daily	75-mg hydralazine plus 40-mg isosorbide three times daily * 300-mg total hydralazine plus 120-mg total isosorbide dinitrate daily in divided doses	Indicated in conjunction with GDMT in patients self-identified as African American with NYHA class III-IV HFrEF to improve symptoms and reduce morbidity and mortality Indicated in current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARNI, ACE inhibitor, or ARB, because of drug intolerance or renal insufficiency to reduce morbidity and mortality

Drug	Initial Dose	Usual Range	PK/PD Considerations, Key Drug Interactions, Other Concerns
Additional Tx for HFrEF or HFpEF or other cardiomyopathies			
Digoxin	**0.125-0.25 mg once daily** **Titrate dose according to age, lean body weight, and renal function;** **individualized, variable dose to** **achieve serum digoxin concentration of** **0.5-0.9 ng/mL (0.6-1.2 nmol/L)**		Indicated in conjunction with GDMT in symptomatic HFrEF despite GDMT (or who are unable to tolerate GDMT) to decrease hospitalizations for HF
Ivabradine	Initiate 5 mg twice daily, increase at 2 weeks to 7.5 mg twice daily to achieve a resting HR of 50-60 beats/min If HR <50 beats/min, may reduce dose to 2.5 mg twice daily Take with food		Indicated with GDMT in symptomatic, NYHA class II-III, stable chronic HFrEF (LVEF ≤35%) including a β-blocker at maximum tolerated dose, and who are in sinus rhythm with an HR ≥70 beats/min at rest, to reduce HF hospitalizations and cardiovascular death Contraindicated with strong CYP3A4 inhibitors Additive risk of bradycardia with other medications with negative chronotropic effects (eg, digoxin)

Drug	Initial Dose	Usual Range	PK/PD Considerations, Key Drug Interactions, Other Concerns
Additional Tx for HFrEF or HFpEF or other cardiomyopathies			
Ferric carboxymaltose (Injectafer)	On day 1: Hgb ≤14 g/dL (140 g/L; 8.69 mmol/L): 1,000 mg, Hgb 14-15 g/dL (140-150 g/L; 8.69-9.31 mmol/L): 500 mg At week 6: If <70 kg, 500 mg if Hgb <10 g/dL (100g/L; 6.21 mmol/L), otherwise no dose If >70 kg, 1,000 mg if Hgb <10 g/dL (100g/L; 6.21 mmol/L), 500 mg if Hgb 10-14 g/dL (100-150 g/L; 6.21-8.69 mmol/L): 100, and no dose if Hgb 14-15 g/dL (140-150 g/L; 8.69-9.31 mmol/L)		Indicated for iron deficiency in adult patients with NYHA class II-III HF to improve exercise capacity Administer a maintenance dose of 500 mg at weeks 12, 24, and 36 if serum ferritin <100 ng/mL (mcg/L; 225 pmol/L) or serum ferritin 100-300 ng/mL (mcg/L; 225-674 pmol/L) and transferrin saturation <20% No dosing data available after 36 weeks or with Hgb ≥15 g/dL (150 g/L; 9.31 mmol/L)

*: Regimens proven in large clinical trials to reduce mortality.

Drug Monitoring Table

Drug Class	Adverse Effect	Monitoring Parameters	Comments
ACEIs	Angioedema, cough, hyperkalemia, hypotension, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with bilateral renal artery stenosis, history of angioedema, or pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1-2 weeks after initiation or increase in dose. Goal is target dose from clinical trials or highest tolerated.
ARBs	Hyperkalemia, hypotension, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with bilateral renal artery stenosis or pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1-2 weeks after initiation or increase in dose. Use with caution in patients with a history of ACEI-associated angioedema. Goal is target dose from clinical trials or highest tolerated.
Sacubitril/ valsartan	Angioedema, hyperkalemia, hypotension, dizziness, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with a history of angioedema associated with ACEI or ARB therapy or in pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1-2 weeks after initiation or dose increase. Start with a low dose and double the dose every 2-4 weeks as tolerated based on BP, serum potassium, and renal function. Goal is target dose from clinical trials or highest tolerated.

Drug Monitoring Table

Drug Class	Adverse Effect	Monitoring Parameters	Comments
Aldosterone antagonists	Gynecomastia/breast tenderness/menstrual irregularities (spironolactone), hyperkalemia, worsening renal function	BP, electrolytes, BUN, and creatinine	Assess BP, BUN, creatinine, and electrolytes at baseline. Check potassium 3 days and 1 week after initiation and then monthly for the first 3 months. Change to eplerenone if gynecomastia develops with spironolactone.
β-blockers	Bradycardia, heart block, bronchospasm, hypotension, worsening HF	BP, HR, ECG, signs and symptoms of worsening HF, blood glucose	Start with low dose and titrate upward no more often than every 2 weeks as tolerated based on BP, HR, and symptoms. Goal is target dose from clinical trials or highest tolerated. Patients may feel worse before they feel better.
Digoxin	GI and CNS adverse effects, brady- and tachyarrhythmias	electrolytes, BUN, creatinine, ECG, serum digoxin concentration	Target serum digoxin concentration 0.5-0.9 ng/mL.
SGLT2i	UTIs, Genital mycotic infections, polyuria, polydipsia, hypotension, dehydration, bone fracture.	Renal function, BP, Lipids, Pregnancy test (before), HbA1c (DM)	Before initiation: 1. Assess renal function beforehand and periodically thereafter 2. Correct condition in patients with volume depletion

Drug Monitoring Table

Drug Class	Adverse Effect	Monitoring Parameters	Comments
Ivabradine	Bradycardia, hypertension, atrial fibrillation, luminous phenomena (phosphenes, transiently enhanced brightness in a portion of the visual field)	BP, HR, ECG	Start with 5 mg twice daily and after 2 weeks adjust dose to achieve a resting HR 50-60 BPM. Only use in patients in sinus rhythm.
Diuretics	Hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, renal dysfunction, thirst	BP, electrolytes, BUN, creatinine, glucose, uric acid, changes in weight, JVD	Dose should be adjusted based on volume status, renal function, electrolytes, and BP. Reassess these parameters 1-2 weeks after dose changes. Goal is lowest dose that maintains euvolemia.
Hydralazine	Hypotension, headache, rash, arthralgia, lupus, tachycardia	BP, HR	
Nitrates	Hypotension, headache, lightheadedness	BP, HR	
Ferric carboxymaltose	Hypersensitivity, hypophosphatemia, HTN, flushing, injection site reaction, erythema, rash, nausea, vomiting, dizziness, headache	Serum ferritin, Hgb, Hct, BP, blood phosphate levels	Observe hypersensitivity during and after administration for at least 30 minutes and until clinically stable following completion of each administration.

➢ Diuretics

- Diuretic therapy, in addition to sodium restriction, is recommended in **all** patients with clinical evidence of fluid retention.

- Once fluid overload has been resolved, many patients require chronic diuretic therapy to maintain euvolemia.

- Diuretics do not prolong survival or alter disease progression, therefore are not considered mandatory therapy (patients who do not have fluid retention would not require diuretic therapy).

- The primary goal of diuretic therapy is to reduce symptoms associated with fluid retention, improve exercise tolerance and quality of life, and reduce hospitalizations from HF.

- Diuretics accomplish this by decreasing pulmonary & peripheral edema (reduction of preload).

- Diuretic therapy must be used carefully because overdiuresis can lead to a reduction in CO, renal perfusion, and symptoms of volume depletion.

- Diuretic therapy is usually initiated in low doses in the outpatient setting, with dosage adjustments based on *symptom assessment* and *daily body weight*.

- Change in body weight is a sensitive marker of fluid retention or loss, and it is recommended that patients monitor their status by taking daily morning body weights. Patients who gain 1 lb/day (0.45 kg) for several consecutive days or 3 to 5 lb (1.4-2.3 kg) in a week should contact their healthcare provider for instructions (which often will be to increase the diuretic dose temporarily).

- Such action often will allow patients to prevent a decompensation that requires hospitalization.

- Hypotension or worsening renal function (eg, increases in serum creatinine) may be indicative of volume depletion and necessitates a reduction in the diuretic dose.

➢ ACEIs:

- ACEI therapy improves symptoms, NYHA functional class, HF progression, hospitalizations, and quality of life in both symptomatic and asymptomatic patients with reduced LVEF

- Improve survival by 20 -30% compared with placebo (benefits maintained with continued therapy)

- Benefits are independent of HF etiology, are greatest in patients with the most severe symptoms, and are likely a “class effect”.

- ACEIs administered after MI improve overall survival, decrease development of severe HF, and reduce reinfarction and HF hospitalization rates (most pronounced in higher-risk patients as symptomatic HF or reduced LVEF)

- Initiation of β-blocker therapy should not be delayed until target ACEI doses are achieved since the addition of a β-blocker is proven to reduce mortality, whereas that is not the case with increasing ACEI doses.

- Asymptomatic hypotension should not be considered a contraindication to starting therapy with an ACEI, although initiation or dose increases in patients with SBP less than 90 to 100 mm Hg should be done cautiously.

- An often overlooked solution to hypotension is to space the administration times of medications (eg, diuretics and β-blockers) throughout the day so that these medications are not all administered at or near the same time.

- Increases in serum creatinine > 0.5 mg/dL if the baseline creatinine is < 2 mg/dL or > 1 mg/dL if the creatinine is > 2 mg/dL should prompt clinicians to reduce the dose of ACEIs or reconsider ACE therapy and evaluate potential causes for the abrupt decline in renal function.

➢ Angiotensin II Receptor Blockers

- ARBs are not an alternative in patients with hypotension, hyperkalemia, or renal insufficiency secondary to ACEIs because they are as likely to cause these adverse effects (similar incidence).

➢ β-Blockers

- β-blockers reduce morbidity and mortality in patients with HFrEF.

- Importantly, it is not essential that ACEI doses be optimized before a β-blocker is started because the addition of a β-blocker is likely to be of greater benefit than an increase in ACEI dose.

- Three β-blockers have been shown to significantly reduce mortality compared with placebo: carvedilol, metoprolol succinate (CR/XL), and bisoprolol.

- The benefits of β-blockade occur regardless of HF etiology or disease severity.

- β-Blockers should be initiated in stable patients who have no or minimal evidence of fluid overload. In unstable patients, other HF therapy should be optimized and then β-blocker therapy reevaluated once stability is achieved.

- Initiation of a β-blocker at normal doses in patients with HF may lead to symptomatic worsening or acute decompensation owing to the drug's negative inotropic effect. For this reason, β-blockers are listed as drugs that may exacerbate or worsen HF.

- To minimize the likelihood for acute decompensation, β-blockers should be started in very low doses with slow upward dose titration and close monitoring.

- β-Blocker doses should be doubled no more often than every 2 weeks, as tolerated, until the target or maximally tolerated dose is reached.

- Clinical trial experience shows that target β-blocker doses can be achieved in the majority of patients provided that appropriate initiation, titration, and education are implemented.

✓ Absolute contraindications to β-blocker use include:
- uncontrolled bronchospastic disease
- symptomatic bradycardia
- advanced heart block without a pacemaker
- acute decompensated HF

✓ β-blockers may be tried with caution in patients with:
- asymptomatic bradycardia
- COPD, or well-controlled asthma
- marked bradycardia (less than 55 beats/min) or hypotension

➢ Aldosterone Antagonists

- In the kidney, aldosterone antagonists inhibit sodium reabsorption and potassium excretion.

- In the heart, aldosterone antagonists inhibit cardiac extracellular matrix and collagen deposition, thereby attenuating cardiac fibrosis and ventricular remodeling.

- Aldosterone antagonists also attenuate the systemic proinflammatory state, atherogenesis, and oxidative stress caused by aldosterone.

- Current guidelines recommend adding a low-dose aldosterone antagonist to standard therapy to improve symptoms, reduce the risk of HF hospitalization, and increase survival in select patients provided that potassium and renal function can be carefully monitored.

- Low-dose aldosterone antagonists are appropriate for two groups of patients, those with:

    1. mild to moderately severe HFrEF (NYHA class II-IV) who are receiving standard therapy
    2. left ventricular dysfunction and either acute HF or diabetes early after MI

- Serum creatinine may overestimate renal function in the elderly and in patients with decreased muscle mass, in whom creatinine clearance should serve as a guide for the appropriateness of aldosterone antagonist therapy.

✓ Initiation of every-other-day dosing is appropriate for patients with marginal renal function or who are otherwise at high risk for hyperkalemia.

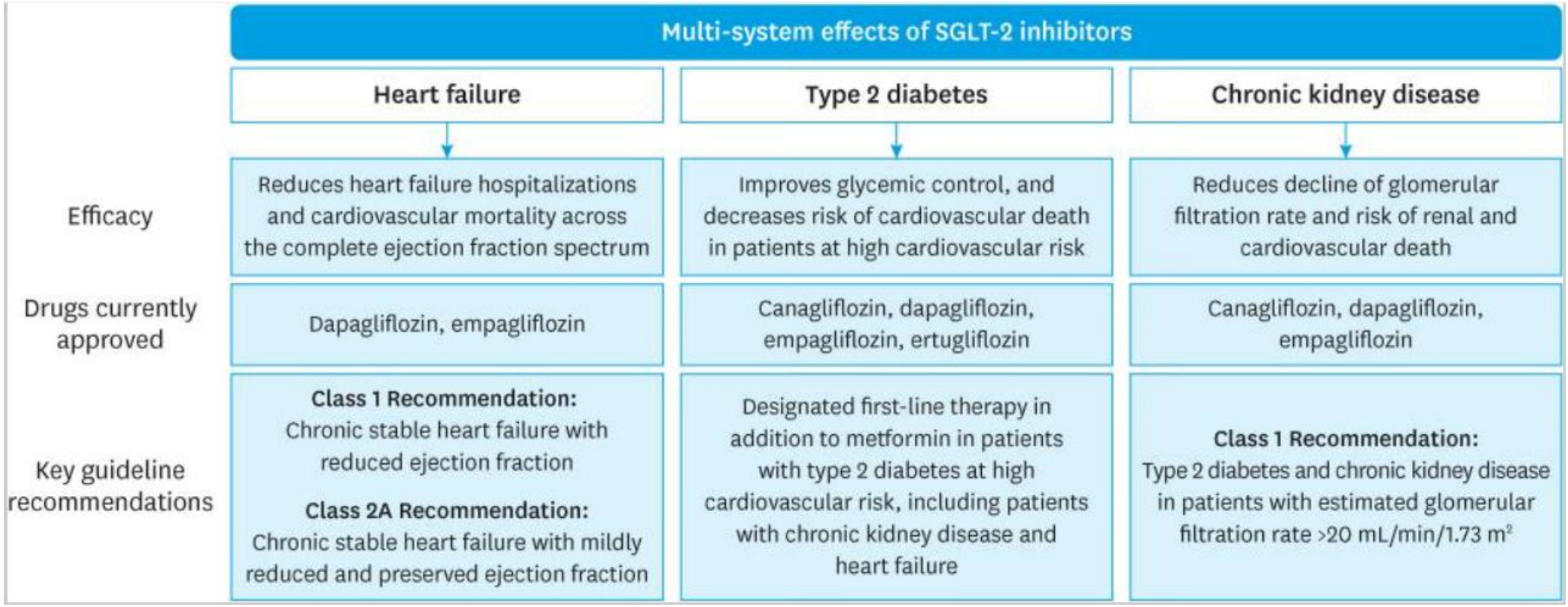
✓ Some recommended strategies for reducing hyperkalemia risk with Aldosterone Antagonists:

1. Avoid starting aldosterone antagonists in patients with any of the following:
   - Serum creatinine > 2.0 in women or > 2.5 mg/dL in men or a CrCl < 30 mL/min/1.73 m^2
   - Recent worsening of renal function
   - Serum potassium concentration > 5.0 mEq/L
   - History of severe hyperkalemia

2. Start with low doses (12.5 mg/day spironolactone & 25 mg/day for eplerenone) especially in the elderly and in those with diabetes or a creatinine clearance <50 mL/min/1.73 m^2.

➢ Sodium Glucose Co-transporter 2 Inhibitor (SGLTi)

The most recent ESC 2021 and AHA/ACC/HFSA 2022 HF guidelines recommend the use of SGLT-2 inhibitors (currently only dapagliflozin and empagliflozin) in the management of chronic, stable HFrEF (class 1 recommendation for a reduction in cardiovascular death and HF hospitalizations) irrespective of baseline diabetes status.



The spectrum of clinical indications of SGLT-2 inhibitors.

Talha KM, Anker SD, Butler J. SGLT-2 Inhibitors in Heart Failure: A Review of Current Evidence. Int J Heart Fail. 2023;5(2):82-90. Published 2023 Mar 13. doi:10.36628/ijhf.2022.0030

➢ Drug Therapies to Consider for Selected Patients with HFrEF

➢ Nitrates and Hydralazine

- Originally combined because of their complementary hemodynamic actions.
- Nitrates result in venodilation and decreased preload.
- Hydralazine is a direct-acting arterial vasodilator causing a decrease in SVR and resultant increases in SV and CO.
- Guidelines recommend the addition of hydralazine/ISDN to African Americans with HFrEF and NYHA class III–IV symptoms treated with ACEIs and β-blockers (a significant 43% reduction in all-cause mortality)

- Hydralazine/ISDN can also be useful in patients unable to tolerate either an ACEI or ARB because of renal insufficiency, or hyperkalemia.

- Obstacles limit the use of hydralazine/ISDN:

1. the need for frequent dosing (fixed-dose combination administered three times daily)

2. adverse effects are common (~30% of patients reporting dizziness, headache & GI distress)

3. the high cost of the BiDil® fixed-dose combination product compared with that of the individual generic drugs purchased separately.

➢ Angiotensin II Receptor Blocker/Neprilysin Inhibitor (ARNI)

- The first angiotensin receptor/neprilysin inhibitor approved for the treatment of patients with HFrEF is valsartan/sacubitril.

- Sacubitril, a neprilysin inhibitor prodrug.

- After ingestion, sacubitril dissociates from the complex and is cleaved into its active form LBQ657, which inhibits the action of neprilysin that degrades natriuretic peptides (NPs) and bradykinin.

- Natriuretic pepetides are beneficial because they cause vasodilation, increase glomerular filtration, natriuresis, diuresis, inhibit renin secretion, aldosterone production and attenuate ventricular hypertrophy and fibrosis.

- The valsartan component of the combination product is 40% to 60% more bioavailable than conventional valsartan tablets. Thus, the 24 mg sacubitril/26 mg valsartan tablet is equivalent to 40 mg of valsartan.

- Sacubitril/valsartan should be avoided in patients with severe hepatic impairment.

- The most common adverse reactions include hypotension, dizziness, hyperkalemia, worsening renal function, and cough.

- Angioedema occurred more frequently with sacubitril/valsartan compared to enalapril.

- Sacubitril/valsartan is contraindicated in patients with history of angioedema associated with an ACEI or ARB.

- Sacubitril/valsartan is also contraindicated in pregnancy and should not be used concurrently with ACEIs or other ARBs.

- BNP concentrations will be “falsely elevated” and cannot be used in monitoring patients.

➢ Ivabradine

- Ivabradine has been recently approved to reduce hospitalizations in patients with HFrEF.

- It is approved for the treatment of patients with HFrEF in sinus rhythm with a HR ≥ 70 bpm that are receiving maximally tolerated treatment with β-blockers or have contraindications to β-blockers.

- Ivabradine does not affect BP, myocardial contractility, or AV conduction.

- Elevated resting HR (> 70-80 bpm) is emerging as an important independent risk factor for adverse outcomes in patients with HF and is associated with increased hospital admissions, disease progression, and mortality.

- The starting dose of ivabradine in most patients is 5 mg twice daily with meals. After 2 weeks of treatment, resting HR should be evaluated and if between 50 and 60 bpm, the dose should be continued.

- If the HR is > 60 bpm, the dose can be increased to the maximum of 7.5 mg twice daily.

- Ivabradine reduced resting heart rate by approximately 11 BPM compared to placebo.

- Co-administration with strong CYP3A4 inhibitors (eg, itraconazole, macrolide antibiotics, HIV protease inhibitors) is contraindicated because of the large increase in exposure and potential for bradycardia or other conduction abnormalities.

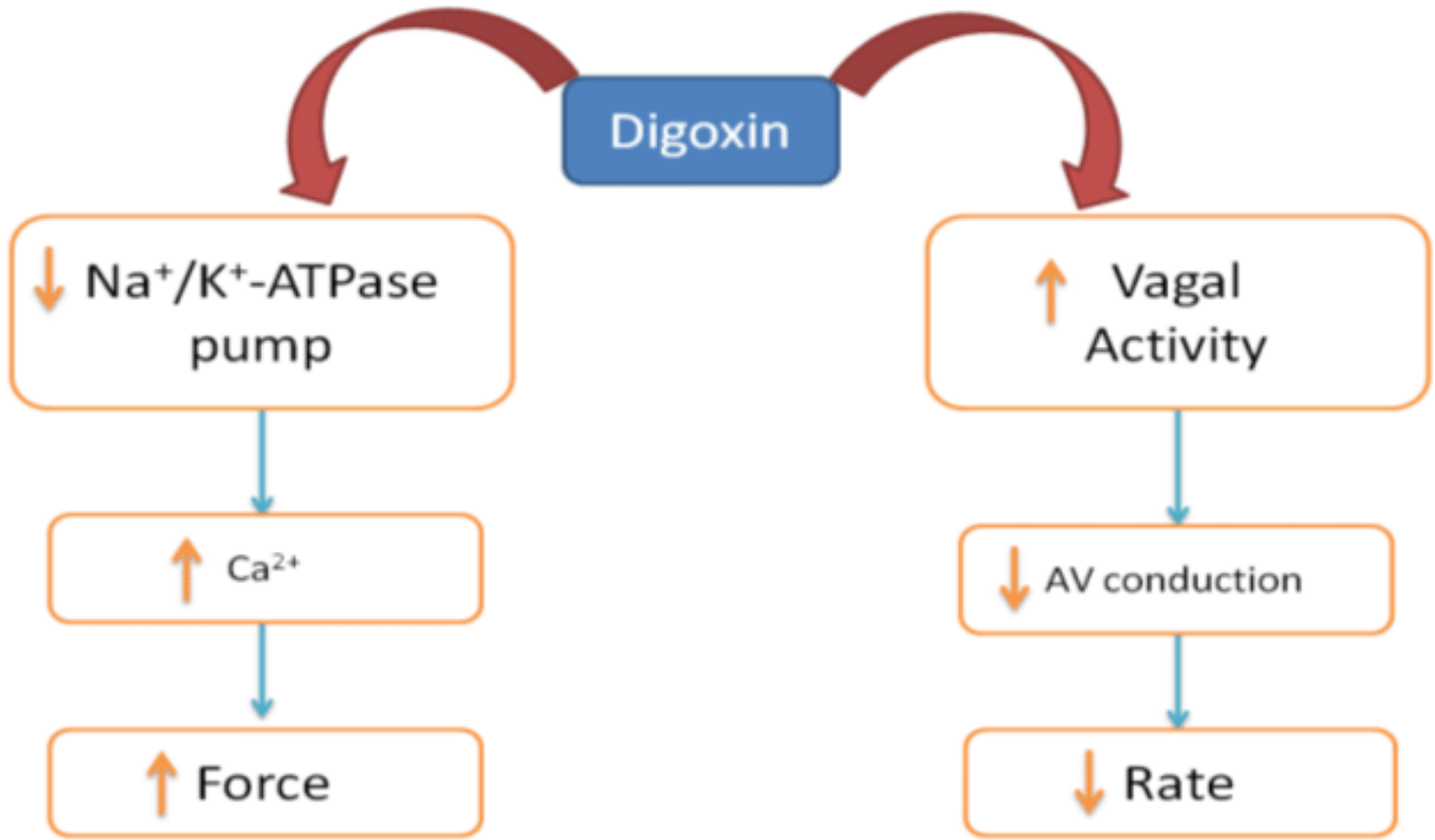
- Moderate CYP3A4 inhibitors (eg, verapamil, diltiazem, grapefruit juice) and inducers (eg, St. John’s wort, rifampin, phenytoin) should be avoided as well.

➢ Digoxin

- 1785 foxglove or Digitalis purpurea

- In 1920s digitalis glycosides were clearly demonstrated to have a positive inotropic effect on the heart.

- In late 1980s, clinical trials were conducted to critically evaluate the role of digoxin in the therapy of chronic HF.


Digoxin
↓ Na⁺/K⁺-ATPase pump
↑ Ca²⁺
↑ Force
↑ Vagal Activity
↓ AV conduction
↓ Rate

- Clinical trials have shown that digoxin improves cardiac function, quality of life, exercise tolerance, and HF symptoms in patients with HFrEF.

- A positive inotropic agent does not increase mortality and actually decreases morbidity in patients with HFrEF. No apparent benefit of digoxin on hospitalizations or mortality in HFpEF.

- The clinical benefits of digoxin are achieved at lower SDCs (between 0.5 and 0.9 ng/mL), with no additional benefit with higher concentrations.

- Patients with decreased renal function or low body weight, the elderly, or those receiving interacting drugs (eg, amiodarone) should receive 0.125 mg daily or every other day.

- Routine measuring of SDCs is not necessary in the absence of suspected digoxin toxicity (worsening renal function, institution of an interacting drug, or other conditions that may significantly affect SDC).

Selected Digoxin Drug Interactions

Drugs	Mechanism/Effect	Suggested Clinical MGT
Amiodarone, dronedarone	Inhibits P-glycoprotein resulting in decrease in renal and nonrenal clearance; can increase SDC by 70%-100%	Monitor SDC and adverse effects; anticipate the need to reduce the dose by 30%-50%
Antacids	Concurrent administration may decrease digoxin bioavailability by 20%-35%	Space doses at least 2 h apart or avoid concurrent use if possible
Cholestyramine, colestipol	Bind digoxin in gut and decrease bioavailability 20%-35%; may also decrease enterohepatic recycling	Space doses at least 2 h apart or avoid concurrent use if possible
Cyclosporine	Inhibits P-glycoprotein resulting in decreased clearance	Monitor SDC and adverse effects; anticipate the need to reduce the dose

Selected Digoxin Drug Interactions

Drugs	Mechanism/Effect	Suggested Clinical MGT
Diuretics	Thiazides or loop diuretics may cause hypokalemia and hypomagnesemia, thereby increasing the risk of digitalis toxicity	Monitor and replace electrolytes if necessary
Erythromycin, clarithromycin, tetracycline	Alter gut bacterial flora; bioavailability and SDC increase 40%-100% in about 10% of patients who extensively metabolize digoxin in the gut, may also be due to inhibition of P-glycoprotein by macrolides	Monitor SDC and anticipate the need to reduce the dose; avoid concurrent use if possible
Ketoconazole, itraconazole	Decrease in renal and nonrenal clearance by inhibition of P-glycoprotein; SDC may increase by 50%-100%	Monitor SDC and anticipate the need to reduce the dose by 50%

Selected Digoxin Drug Interactions

Drugs	Mechanism/Effect	Suggested Clinical MGT
Metoclopramide	Increase in gut mobility may decrease bioavailability of slow dissolving tablets; unknown significance	Effect is minimized by administration of digoxin capsules
Propafenone	Decrease in renal clearance; SDC may increase 30%-40%	Monitor SDC and anticipate the need to reduce the dose
Ritonavir, telaprevir	Inhibits P-glycoprotein and may increase SDC	Monitor SDC and anticipate the need to reduce the dose
Verapamil	Inhibits P-glycoprotein resulting in decrease in renal and nonrenal clearance, SDC may increase 70%-100%	Monitor SDC and anticipate the need to reduce the dose by 50%; consider using another calcium channel blocker

Selected Digoxin Drug Interactions

Drugs	Mechanism/Effect	Suggested Clinical MGT
Quinidine	Inhibits P-glycoprotein resulting in decrease in renal and nonrenal clearance; also displacement of digoxin from tissue binding sites with decrease in the volume of distribution; SDC generally increases about twofold	Monitor SDC and adverse effects; anticipate the need to reduce dose by 50%
Spironolactone	Decrease in renal and nonrenal clearance; also interference with some digoxin assays thus increasing apparent SDC	Monitor SDC and anticipate the need to reduce dose; check assay for interference

- Adverse effects

- Usually well tolerated by most patients
- Noncardiac adverse effects frequently involve the CNS or GI systems but also may be nonspecific (eg, fatigue or weakness).
- Cardiac manifestations include numerous different arrhythmias. Cardiac arrhythmias may be the first evidence of toxicity in a patient (before any noncardiac symptoms occur).
- Patients at increased risk of toxicity include those with impaired renal function, decreased lean body mass, the elderly, and those taking interacting drugs.
- Hypokalemia, hypomagnesemia, and hypercalcemia will predispose patients to cardiac manifestations of digoxin toxicity.

- Hypothyroidism, myocardial ischemia, and acidosis will also increase the risk of cardiac adverse effects.

- Although digoxin toxicity is commonly associated with plasma concentrations greater than 2 ng/mL, toxicity may occur at lower concentrations and clinicians should remember that digoxin toxicity is based on the presence of symptoms rather than a specific plasma concentration.

- Usual treatment of digoxin toxicity includes drug withdrawal or dose reduction and treatment of cardiac arrhythmias and electrolyte abnormalities.

- In patients with life-threatening digoxin toxicity, purified digoxin-specific Fab antibody fragments should be administered. SDCs will not be reliable until the antidote has been eliminated from the body.

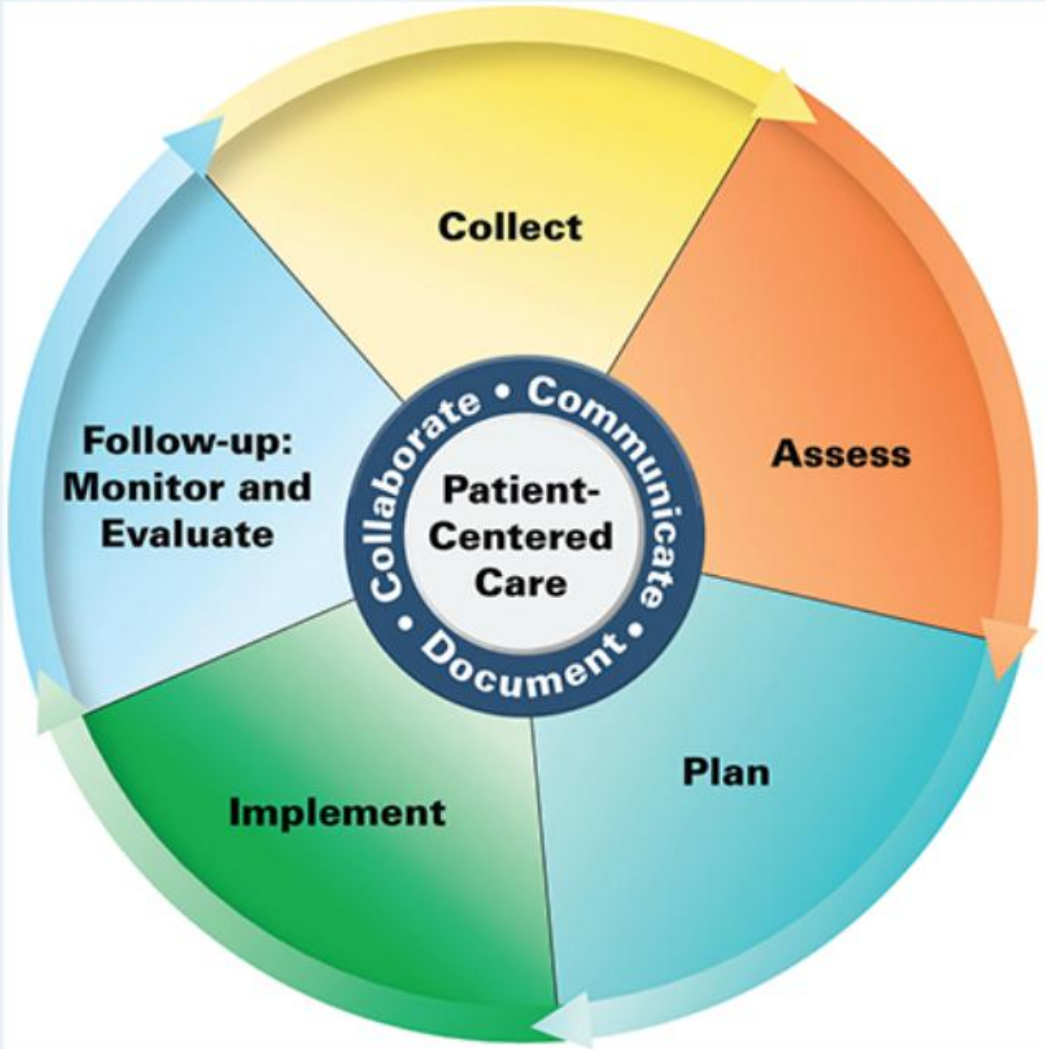
- Signs and Symptoms of Digoxin Toxicity

- Noncardiac (mostly CNS) adverse effects:
  - Fatigue, weakness, dizziness, headache, neuralgia, confusion, delirium, psychosis
  - Anorexia, nausea, vomiting, abdominal pain
  - Visual disturbances (Halos, photophobia, problems with color perception (ie, red-green or yellow-green vision)

- Cardiac adverse effects [a,b]:
  - Ventricular arrhythmias
  - Atrioventricular (A-V) block
  - Paroxysmal atrial tachycardia with A-V block
  - Sinus bradycardia

a:Some adverse effects may be difficult to distinguish from the signs/symptoms of heart failure.
b: Digoxin toxicity has been associated with almost every known rhythm abnormality (only the more common manifestations are listed).

Patient Care Process for Heart Failure



Collect

- Patient characteristics (eg, age, sex)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use) and dietary habits including intake of sodium-containing foods
- Current medications including over-the-counter, herbal products, dietary supplements
- Etiology of HF (Table 39-1)
- Objective data
  - BP, HR, respiratory rate, height, weight, LVEF, ECG, chest x-ray
  - Labs including complete blood count, comprehensive metabolic panel (eg, serum sodium, potassium, blood urea nitrogen (BUN), creatinine, urinalysis, liver function tests, thyroid-stimulating hormone, iron studies (serum ferritin and transferrin saturation), BNP, or NT-proBNP
  - Physical examination (eg, signs/symptoms of volume overload [see the "Clinical Presentation" box])

Assess

- Hemodynamic stability (eg, systolic BP <90 mm Hg, signs/symptoms of hypotension or poor perfusion)
- Presence of comorbidities (eg, CAD, HTN, diabetes, AF)
- Presence of volume overload (eg, weight gain, rales, JVD, peripheral edema)
- Presence of exertional dyspnea, orthopnea, fatigue
- Emotional status (eg, presence of anxiety, depression)

Plan*

- HFrEF
  - Initiate and titrate GDMT with angiotensin-receptor blocker/neprilysin inhibitor (ARNI)/ACE inhibitor/angiotensin receptor blocker (ARB) + guideline-directed β-blocker + mineralocorticoid receptor antagonist (MRA) + SGLT2 inhibitor (Tables 39-6 and 39-7). ARNI is preferred over ACE inhibitor and ARB. Add diuretics if the patient is volume overloaded.
  - Add additional drug therapy as indicated based on patient characteristics (eg, isosorbide dinitrate [ISDN]/hydralazine, ivabradine, digoxin, vericiguat [Fig. 39-6 and 39-7; Tables 39-6 and 39-7])
- HFpEF
  - Initiate and titrate GDMT with SGLT2 inhibitor + ARNI + MRA in select patients (Fig. 39-8; Tables 39-6 and 39-7). Add diuretics if the patient is volume overloaded.
- Monitoring parameters include efficacy by improvement of symptoms (eg, shortness of breath, lower extremity edema, pulmonary congestion), safety by avoidance of adverse drug effects (eg, worsening renal function, hypotension, bradycardia [if prescribed β-blocker, ivabradine, or digoxin], hyperkalemia), and follow-up frequency and timing
- Patient education (eg, the purpose of treatment, dietary and lifestyle modification, drug-specific information including adverse effects, medication administration)
- Self-monitoring for HF symptoms (eg, daily weights, sodium, and fluid intake)
- Referrals to other providers when appropriate (eg, HF specialist for consideration of advanced therapies [HFrEF], electrophysiologist for placement of ICD [HFrEF, secondary prevention of sudden cardiac death in select patients with HFpEF] and/or CRT [HFrEF], dietician)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, serum creatinine, electrolytes, vital signs, adherence assessment)

Follow-up: Monitor and Evaluate

- Resolution of HF signs and symptoms (eg, JVD, weight, shortness of breath)
- Evaluate the need for dose titration of GDMT and/or the initiation of additional therapies
- Presence of adverse effects (eg, serum creatinine, electrolytes, BP, HR)
- Patient adherence to treatment plan using multiple sources of information

****Collaborate with the patient, caregivers, and other healthcare professionals.***

Thank you