Treatment of chronic heart failure

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1. How are heart failure symptoms classified?

Symptoms are most commonly classified using the New York Heart Association (NYHA) classification system:

- Class I: No limitation; ordinary physical activity does not cause excess fatigue, shortness of breath, or palpitations.
- Class II: Slight limitation of physical activity; ordinary physical activity results in fatigue, shortness of breath, palpitations, or angina.
- Class III: Marked limitation of physical activity; ordinary activity will lead to symptoms.
- Class IV: Inability to carry on any physical activity without discomfort; symptoms of congestive heart failure are present even at rest; increased discomfort is experienced with any physical activity.

2. What is the stage system for classifying heart failure?

- Stage A: Patient at high risk for developing heart failure but without structural heart disease or symptoms of heart failure. Includes patients with hypertension, coronary artery disease (CAD), obesity, diabetes, history of drug or alcohol abuse, history of rheumatic fever, family history of cardiomyopathy, and treatment with cardiotoxins.
- Stage B: Patient with structural heart disease but without signs or symptoms of heart failure. Includes patients with previous myocardial infarction (MI), left ventricular (LV) remodeling including left ventricular hypertrophy (LVH) and low ejection fraction (EF), and asymptomatic valvular disease.
- Stage C: Patient with structural heart disease with prior or current symptoms of heart failure.
- Stage D: Patient with refractory heart failure requiring specialized interventions.

3. Which medical treatments have been shown to decrease mortality in patients with heart failure?

Pharmacotherapies that have been shown to decrease mortality in patients with HFrEF include the following.

- Angiotensin-converting enzyme (ACE) inhibitors are first-line agents in those with depressed EF because they have been convincingly shown to improve symptoms, decrease hospitalizations, and reduce mortality. Angiotensin II receptor blockers (ARBs) are used in those who are ACEinhibitor intolerant because of persistent cough or in some cases after an episode of angioedema.

- The beta-blockers metoprolol succinate (Toprol XL), carvedilol (Coreg), and bisoprolol have been shown to decrease mortality in appropriately selected patients. These agents should be initiated in euvolemic patients on stable background heart failure therapy, including ACE inhibitors or ARBs.
- Hydralazine (H) and isosorbide (I) are used in patients who are unable to tolerate both ACE inhibitors and ARBs because of renal failure or as a consideration for add-on therapy. H and I should be considered in addition to an ACE inhibitor or ARB in African Americans because they appear to have an added mortality benefit and can be considered as an add-on therapy in others if the patient's blood pressure allows. They may be considered in patients who are ACE-inhibitor and ARB intolerant.
- The aldosterone antagonists, spironolactone or eplerenone, are recommended as additional therapy in carefully selected patients with preserved renal function already on standard heart failure therapies. These agents have an additive decrease in mortality in patients with NYHA class II to IV heart failure symptoms.

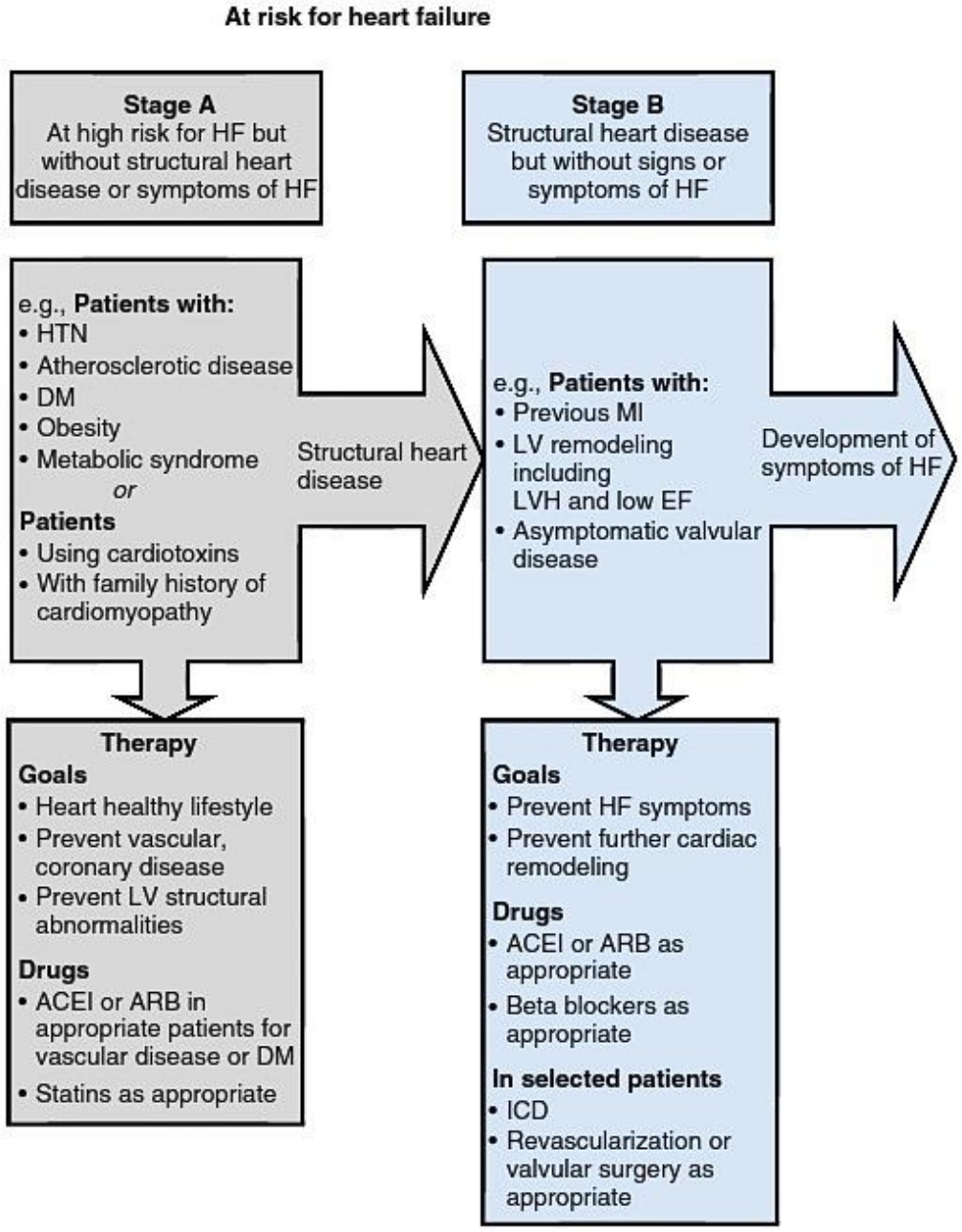

Fig. 27.1. The 2013 ACC/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults. The figure was created before approval of sacubitril/valsartan and ivabradine, which would now be included under Stage C, HFrEF therapies. *(Reproduced from Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Jr., Drazner, M. H., et al. [2013]. 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.* Journal of the American College of Cardiology, 62*[16], e148–e239.)*

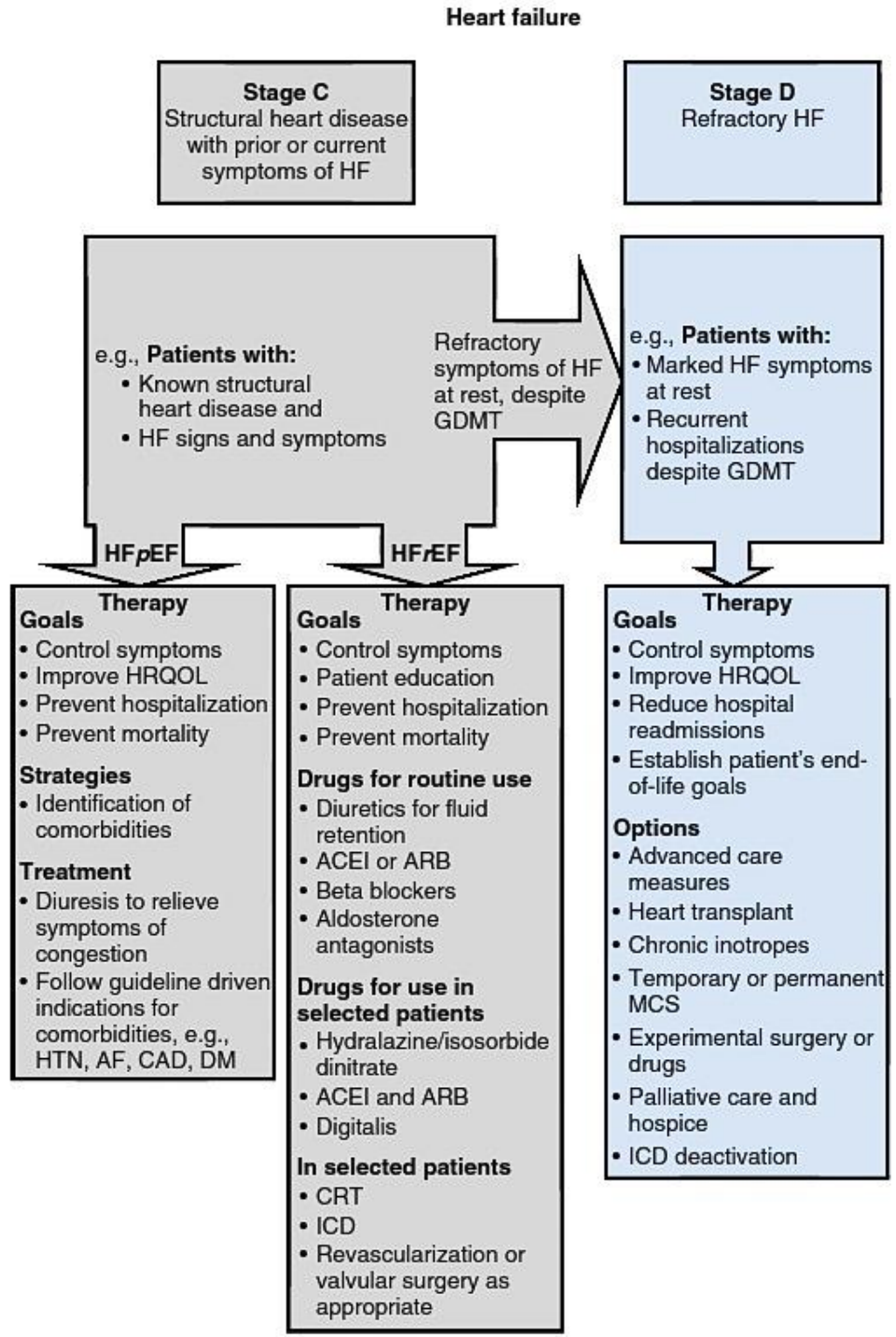
Heart failure
Stage C
Structural heart disease with prior or current symptoms of HF
Stage D
Refractory HF
e.g., Patients with:
• Known structural heart disease and
• HF signs and symptoms
Refractory symptoms of HF at rest, despite GDMT
e.g., Patients with:
• Marked HF symptoms at rest
• Recurrent hospitalizations despite GDMT
HFpEF
HFrEF
Therapy
Goals
• Control symptoms
• Improve HRQOL
• Prevent hospitalization
• Prevent mortality
Strategies
• Identification of comorbidities
Treatment
• Diuresis to relieve symptoms of congestion
• Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
Therapy
Goals
• Control symptoms
• Patient education
• Prevent hospitalization
• Prevent mortality
Drugs for routine use
• Diuretics for fluid retention
• ACEI or ARB
• Beta blockers
• Aldosterone antagonists
Drugs for use in selected patients
• Hydralazine/isosorbide dinitrate
• ACEI and ARB
• Digitalis
In selected patients
• CRT
• ICD
• Revascularization or valvular surgery as appropriate
Therapy
Goals
• Control symptoms
• Improve HRQOL
• Reduce hospital readmissions
• Establish patient's end-of-life goals
Options
• Advanced care measures
• Heart transplant
• Chronic inotropes
• Temporary or permanent MCS
• Experimental surgery or drugs
• Palliative care and hospice
• ICD deactivation

Table 27.1. Magnitude of Benefit of Specific Medical Therapy as Demonstrated by Clinical Trials

MEDICAL THERAPY	RELATIVE RISK REDUCTION IN MORTALITY	NUMBER NEEDED TO TREAT FOR MORTALITY REDUCTION	RELATIVE RISK REDUCTION IN HEART FAILURE HOSPITALIZATIONS (%)
ACE inhibitors or ARBs	17	26	31
Beta-blocker	39	4	41
Aldosterone antagonist	30	6	35
Hydralazine/nitrate	43	7	33

ACE, *Angiotensin-converting enzyme*; ARBs, *angiotensin II receptor blockers*.

Adapted from Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Jr., Drazner, M. H., *et al.* [2013]. *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*. Journal of the American College of Cardiology, 62[16], e148–e239.

Table 27.2. Initial and Target Doses for Commonly Utilized Drugs for Patients with Depressed Systolic Ejection Fraction and/or Congestive Heart Failure

DRUG	INITIAL DAILY DOSES	TARGET/MAXIMUM DOSES
Angiotensin Converting Enzyme Inhibitors		
Captopril	6.25 mg TID	50 mg TID
Enalapril	2.5 mg BID	10-20 mg BID
Lisinopril	2.5-5 mg qD	20-40 mg qD
Perindopril	2 mg qD	8-16 mg qD
Ramipril	1.25-2.5 mg qD	10 mg qD
Trandolapril	1 mg qD	4 mg qD
Angiotensin Receptor Blockers		
Candesartan	4-8 mg qD	32 mg qD
Valsartan	20-40 mg BID	160 mg BID
Angiotensin Receptor Neprilysin Inhibitor		
Sacubitril/valsartan	24/26-49/51 mg BID	97/103 mg BID
Aldosterone Antagonists		
Spironolactone	12.5-25 mg qD	25 mg qD
Eplerenone	25 mg qD	50 mg qD
Beta-Blockers		
Bisoprolol	1.25 mg qD	10 mg qD
Carvedilol	3.125 mg BID	25 mg BID (50 mg BID if >85 kg)
Metoprolol succinate	12.5-25 mg qD	200 mg qD
Cyclic Nucleotide-Gated Channel Blocker		
Ivabradine	2.5-5 mg BID	2.5-7.5 mg BID (based on HR)
Loop Diuretics		
Bumetanide	0.5-1.0 mg qD-BID	Max daily dose 10 mg
Furosemide	20-40 mg qD-BID	Max daily dose 600 mg
Torsemide	10-20 mg qD	Max daily dose 200 mg
Thiazide Diuretics		
Chlorothiazide	250-500 mg qD-BID	Max daily dose 1000 mg
Chlorthalidone	12.5-25 mg qD	Max daily dose 100 mg
Hydrochlorothiazide	25 mg qD-BID	Max daily dose 200 mg
Metolazone	2.5 mg qD	Max daily dose 20 mg
Potassium-Sparing Diuretics		
Amiloride	5 mg qD	Max daily dose 20 mg
Eplerenone	25 mg qD	50 mg qD
Spironolactone	12.5-25 mg qD	Max daily dose 50 mg
Triamterene	50-75 mg BID	Max daily dose 200 mg

Adapted from Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Jr., Drazner, M. H., et al. [2013]. 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. Journal of the American College of Cardiology, *62[16], e148–e239.*

ICDs are considered for primary prevention of sudden cardiac death in patients whose EF remains less than 30% to 35% despite optimal medical therapy and who have a good-quality life expectancy of at least 1 year.

- Biventricular pacing for resynchronization therapy. According to 2013 ACCF/AHA guidelines biventricular pacing (BiV) or cardiac resynchronization therapy (CRT) should be considered for patients in sinus rhythm with NYHA class II to IV symptoms, left ventricular ejection fraction (LVEF) less than 35%, and QRS greater than 150 ms. Consultation with an electrophysiologist is recommended.

In July 2015 a new agent was approved by the FDA, which included a combination of a neprilysin-inhibitor; sacubitril; and an ARB, valsartan. This agent was the first to show a decrease in hospitalization and mortality versus traditional ACE inhibitor therapy as demonstrated in the PARADIGM-HF study. It should be started in patients with NYHA class II to IV heart failure symptoms with reduced EF and who are either not already on an ACE inhibitor/ARB or in substitution for current ACE inhibitor/ARB therapy.

4. What is the suggested dosing regimen of sacubitril and valsartan?

For patients being switched from an ACE inhibitor to sacubitril/valsartan, the product package insert recommended starting dose is 49/51 mg (sacubitril/valsartan) twice daily. A washout period of 36 hours between discontinuation of the ACE inhibitor and initiation of sacubitril/valsartan is recommended. It is recommended to double the dose of the drug combination after 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated. It is recommended that the starting dose be reduced to 24/26 mg twice daily for:

- Patients not currently taking an ACE inhibitor or ARB or previously taking a low dose of these agents
- Patients with severe chronic kidney disease (eGFR <30 mL/min/1.73 m2)
- Patients with moderate hepatic impairment Sacubitril/valsartan should not be used in patients with severe liver disease, pregnancy, concomitant use of ACE inhibitors (allow a washout period of 36 hours), and those with a history of angioedema related to previous ACE inhibitor or ARB therapy. Important side effects of the drug combination include hyperkalemia, renal impairment, hypotension, and angioedema.

5. Which therapies in heart failure have been shown to reduce hospitalization?

All the previously mentioned medical therapies reduce heart failure symptoms and to a degree heart failure hospitalizations. There are also two other medications that appear to impact only heart failure hospitalization. Digoxin has been shown to decrease heart failure symptoms and long-term risk of re-hospitalization in patients already on medical therapy. The Digitalis Investigation Group (DIG) trial was a multicenter, randomized, double-blinded, placebo-controlled study of 6801 symptomatic patients with heart failure and EF less than 45%

Digoxin did not improve total mortality or deaths from cardiovascular causes. However, hospitalizations as a result of worsening heart failure (a secondary endpoint) were significantly reduced by digoxin

Ivabradine was a medication introduced in April 2015 as a new therapy for those with chronic systolic heart failure (LVEF less than 35%), already on maximally tolerated beta-blocker doses, but with persistent resting heart rates over 70 beats per minute. In the randomized SHIFT study it was found to decrease hospitalization from heart failure.

6. What is the suggested dosing regimen of ivabradine?

ivabradine is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with LVEF ≤35% who are in sinus rhythm with a resting heart rate ≥70 beats/min and either are on maximally tolerated doses of betablockers or have a contraindication to beta-blocker use. Contraindications to ivabradine include acute decompensated heart failure, hypotension, sick sinus syndrome, third-degree heart block (unless a pacemaker is present), resting heart rate less than 60 beats/ min, severe liver disease, and pacemaker dependence (heart rate maintained exclusively by a pacemaker). The recommended starting dose of ivabradine is 5 mg twice daily. After 2 weeks of treatment, the dose can be adjusted based on heart rate. The maximum drug dose is 7.5 mg twice daily. In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, the initial recommended dose is 2.5 mg twice daily. Suggested dose adjustments are as follows:

- For HR greater than 60 beats/min, increase dose by 2.5 mg (given twice daily) up to a maximum dose of 7.5 mg twice daily.
- For HR 50 to 60 beats/min, maintain current dose.
- For HR less than 50 beats/min or signs/symptoms of bradycardia, decrease dose by 2.5 mg (given twice daily). If current dose is 2.5 mg twice daily, discontinue therapy.

7. How do angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers work?

ACE inhibitors inhibit ACE, thus blocking the conversion of angiotensin I to angiotensin II. ACE is predominantly found in the pulmonary and to a lesser extent in the renal endothelium. By decreasing the production of angiotensin II, ACE inhibitors attenuate sympathetic tone, decrease arterial vasoconstriction, and attenuate myocardial hypertrophy. Because angiotensin II stimulates aldosterone production, circulating levels of aldosterone are reduced. This results in decreased sodium chloride absorption, decreased potassium excretion in the distal tubules, and decreased water retention. Through a decrease in antidiuretic hormone (ADH) production, ACE inhibitors also decrease water absorption in the collecting ducts. ARBs selectively block the binding of angiotensin II to the AT1 receptor, thereby blocking the effect of angiotensin II on end organs.

8. What approach should be taken if a patient treated with an angiotensinconverting enzyme inhibitor develops a cough?

Nonproductive cough related to ACE inhibitors occurs in 5% to 10% of white patients of European descent and in up to 50% of Chinese patients. The cough is believed related to kinin potentiation. The cough usually develops within the first months of therapy and disappears within 1 to 2 weeks of discontinuation of therapy. ACC/AHA guidelines suggest one should first make sure the cough is related to treatment and not another condition. The guidelines state that the demonstration that the cough disappears after drug withdrawal and recurs after re-challenge with another ACE inhibitor strongly suggests that ACE inhibition is the cause of the cough. They emphasize that patients should be re-challenged, because many will not redevelop a cough, suggesting the initial development of cough was coincidental and may have been related to heart failure. Patients who do have ACE inhibitor--related cough and cannot tolerate symptoms should be treated with an ARB.

9. How do aldosterone antagonists work?

Aldosterone receptor blockers block the mineralocorticoid receptor in the distal renal tubules, thereby decreasing sodium chloride absorption, potassium excretion, and water retention. In addition, they block the direct deleterious effects of aldosterone on the myocardium and may thus decrease myocardial fibrosis and its consequences.

10. Whats two primary indications of aldosterone antagonists in heart failure?

Current primary indications of aldosterone antagonists in heart failure include the following:

- Chronic NYHA class II to IV heart failure and LV EF 35% or less in patients who are already receiving standard therapy for heart failure, including ACE inhibitors, beta-blockers, and diuretics (based on the evaluation of spironolactone in the RALES trial and eplerenone in the EMPHASIS trial)
- Post-MI patients with LV dysfunction (EF less than 40%) and heart failure symptoms who are already receiving standard therapy, including ACE inhibitors and beta-blockers (EPHESUS study of eplerenone)

11. What is the recommended dosing of aldosterone antagonists in heart failure?

Dosing of aldosterone antagonists in heart failure is as follows:

- Spironolactone: 12.5 to 25 mg daily, increased to up to 25 mg twice daily
- Eplerenone: 25 mg daily, increased to 50 mg daily

12. Can all patients with heart failure safely be started on an aldosterone antagonist?

No. Aldosterone antagonists should not be started in

- Men with creatinine more than 2.5 mg/dL or women with creatinine more than 2 mg/dL
- Patients with potassium more than 5 mEq/L
- Those in whom monitoring for hyperkalemia and renal function is not anticipated to be feasible
- Those not already on other diuretics

13. Describe common adverse effects of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone antagonists?

- ACE inhibitors: Hypotension, worsening renal function, hyperkalemia, cough, and angioedema
- ARBs: Hypotension, worsening renal function, and hyperkalemia
- Aldosterone antagonists: Hyperkalemia, worsening renal dysfunction, hypotension, and hyponatremia
- ARBs are as likely as ACE inhibitors to produce hypotension, worsening renal function, and hyperkalemia. Otherwise, ARBs are better tolerated than ACE inhibitors. The incidence of cough is much lower in ARBs (approximately 1%) compared with ACE inhibitors (approximately 10%). The incidence of angioedema with ACE inhibitors is rare (less than 1%; more common in African Americans) and even rarer with ARBs. However, because there have been case reports of patients developing angioedema on ARBs, the guidelines advise that ARBs may be considered in patients who have had angioedema while taking an ACE inhibitor, albeit with extreme caution. Practically, if a patient develops angioedema while taking an ACE inhibitor, an ARB is generally not initiated. Gynecomastia and other antiandrogen effects can occur with spironolactone and are not generally seen with eplerenone.

14. What are the indications for combination therapy with nitrates plus hydralazine in patients with chronic heart failure?

The vasodilator combination of I/H has been shown to produce modest benefits in patients with heart failure compared with placebo. The combination has, however, been shown to be less effective than ACE inhibitors. The A-Heft trial, which was limited to African American patients with class III and IV heart failure, showed that the addition of I/H to standard therapy with an ACE inhibitor or a betablocker conferred significant morbidity and mortality benefit. Taking all the study data together, the I/H combination is indicated in the following patients:

- Those who cannot take an ACE inhibitor or ARB because of renal insufficiency or hyperkalemia
- Those who are hypertensive/symptomatic despite taking ACE inhibitor, ARB, and beta-blockers
- The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African Americans with moderate to severe symptoms on optimal medical therapy with ACE inhibitors, beta-blockers, and diuretics.

15. What dosing is used in treating patients with nitrates and hydralazine?

- Hydralazine: Start at 37.5 mg three times a day, and increase to a goal of 75 mg three times a day.
- Isosorbide dinitrate: Start at 20 mg three times a day, and increase to a goal of 40 mg three times a day.

16. How should patients be treated with beta-blockers?

Certain beta-blockers have been convincingly shown to decrease mortality in patients with depressed EF and symptoms of heart failure, and thus it is a class I indication to treat such patients with betablockers, with an attempt to reach target doses. The beta-blockers shown to decrease mortality, their starting doses,

Recommendations from the Heart Failure Society of America and other organizations include the following:

- Patients should not be initiated on beta-blocker therapy during decompensated or hemodynamically unstable heart failure
- Beta-blocker therapy should only be initiated when patients are euvolemic and hemodynamically stable, are usually on a good maintenance dose of diuretics (if indicated), and receiving ACE inhibitors or ARBs
- Beta-blockers should be initiated at low doses, uptitrated gradually (in at least 2-week intervals), and titrated to target doses shown to be effective in clinical trials. Practitioners should aim to achieve target doses in 8 to 12 weeks from initiation of therapy and to maintain patients at maximal tolerated doses

- If patient symptoms worsen during initiation or dose titration, the dose of diuretics or other concomitant vasoactive medications should be adjusted, and titration to target dose should be continued after the patient's symptoms return to baseline
- If uptitration continues to be difficult, the titration interval can be prolonged, the target dose may have to be reduced, or the patient should be referred to a heart failure specialist
- If an acute exacerbation of chronic heart failure occurs, therapy should be maintained if possible; the dose can be reduced if necessary, but abrupt discontinuation should be avoided. If the dose is reduced (or discontinued), the beta-blocker (and prior dose) should be gradually reinstated before discharge if possible.

17. What diuretics should be used and at what doses should they be initiated in heart failure patients?

Diuretics are indicated for volume overload. Starting doses of furosemide are often 20 to 40 mg once or twice a day, but higher doses will be required in patients with significant renal dysfunction. The dose should be uptitrated to a maximum of up to 600 mg daily

Failure of therapy is often the result of inadequate diuretic dosing. Torsemide is more expensive than furosemide but has superior absorption and longer duration of action. Bumetanide is approximately 40 times more potent milligram-for-milligram than furosemide. It can also be used in patients who are unresponsive or poorly responsive to furosemide, as it is thought to have better absorption. Synergistic diuretics that act on the distal portion of the tubule (thiazides, such as metolazone, or potassium-sparing agents) are often added in those who fail to respond to high-dose loop diuretics alone.

18. Should all heart failure patients be placed on statins?

While statins have been shown to have significant effects in reducing the rate of MI and progression of vascular disease in those with coronary or peripheral vascular disease, the benefits have not been translated to heart failure patients with such atherosclerotic disease. Two large clinical trials, the CORONA trial and the GISSI-HF trial, demonstrated no clinical benefit in the use of statin therapy in addition to recommended medical therapy. Of note, the CORONA trial excluded patients with a history of MI within 6 months and those with a prior percutaneous coronary intervention or stroke but still noted to significantly decrease cardiovascular and heart failure hospitalization in those on statin therapy. The 2013 ACC/AHA guidelines do not currently recommend statin therapy in heart failure patients unless there is another indication.

19. What is the mechanism of action of digoxin?

Digoxin is a cardiac glycoside and is an inhibitor of the Na+-K+ ATPase pump in the sarcolemmal membrane of the myocyte and other cells. This inhibition causes intracellular accumulation of Na+, which makes the Na+-Ca2+ pump extrude less Ca2+, causing Ca2+ to accumulate inside the cell. This effect results in increased force of contraction. Cardiac glycosides also have effects in the central nervous system, enhancing parasympathetic and reducing sympathetic outputs to the heart, through carotid sinus baroreflex sensitization. This is the mechanism that underlies the reduction in sinus node activity and slowing in atrioventricular (AV) conduction, which makes digoxin the only agent with a positive inotropicbradycardic effect and is the basis for its use in the control of some supraventricular arrhythmias.

20. What are some of the relevant drug interactions of digoxin?

Relevant drug interactions of digoxin include the following:

- Quinidine, verapamil, amiodarone, propafenone, and quinine (used for muscle cramps) may double digoxin levels, and the dose of digoxin should be halved when used in combination with any of these drugs.
- Tetracycline, erythromycin, and omeprazole can increase digoxin absorption, whereas cholestyramine and kaolin-pectin can decrease it.
- Thyroxine and albuterol increase the volume of distribution, resulting in decreased levels.
- Cyclosporine and paroxetine and other selective serotonin reuptake inhibitors (SSRIs) can increase serum digoxin levels.

21. What are the clinical manifestations of digoxin toxicity?

Digoxin has a narrow safety margin. (The difference in plasma drug concentrations between therapeutic and toxic levels is small.) Patients with digoxin toxicity may manifest nausea, vomiting, anorexia, diarrhea, fatigue, generalized malaise, visual disturbances (green or yellow halos around lights and objects), and arrhythmias. In the presence of hypokalemia, digoxin toxicity may occur within the therapeutic level. Digoxin dose should be reduced in elderly patients, in patients with renal insufficiency (glomerular filtration rate [GFR] less than 60 mL/min), and when combined with certain drugs. To guide dosing during chronic therapy, digoxin levels should be measured 6 to 8 hours after a dose.

22. What are the electrocardiographic findings of digoxin toxicity?

Digoxin toxicity can result in a variety of ventricular and supraventricular arrhythmias and AV conduction abnormalities. These arrhythmias result from the electrophysiologic effects of digoxin: Increased intracellular Ca2+ levels predispose to Ca2+-induced delayed afterdepolarizations and hence increased automaticity (especially in the junction, Purkinje system, and ventricles); excessive vagal effects predispose to sinus bradycardia/arrest and AV block. Bradyarrhythmias and blocks are more common when the patient is also taking amiodarone. Specific ECG findings include the following:

- Sinus bradycardia
- Sinus arrest
- First- and second-degree AV block
- AV junctional escape
- Paroxysmal atrial tachycardia with AV block
- Bidirectional ventricular tachycardia (VT)
- Premature ventricular beats
- Bigemin
- Regularized atrial fibrillation or atrial fibrillation with slow ventricular response (common)

23. How is digoxin toxicity treated?

It depends on the clinical severity. Digoxin withdrawal is sufficient with only suggestive symptoms. Activated charcoal may enhance the gastrointestinal (GI) clearance of digoxin if given within 6 hours of ingestion. Drugs that increase plasma digoxin levels should be discontinued (except amiodarone because of its long half-life). Correction of hypokalemia is vital (intravenous [IV] replacement through a large vein is preferred with life-threatening arrhythmias), but judgment is needed in the presence of high degrees of AV block. Symptomatic AV block may respond to atropine or to phenytoin (100 mg IV every 5 minutes up to 1000 mg until response or side effects); if no response, use Digibind. The use of temporary transvenous pacing should be avoided. Patients with severe bradycardia should be given Digibind, even if they respond to atropine. Lidocaine and phenytoin may be used to treat ventricular arrhythmias, but for potentially life-threatening bradyarrhythmias or tachyarrhythmias, Digibind should be used. Dialysis has no role because of the high tissue binding of digoxin.

24. What are the indications for Digibind?

The indications for Digibind include life-threatening bradyarrhythmias and tachyarrhythmias; hemodynamic instability caused by digoxin; potassium level of more than 5 mEq/L in the setting of acute ingestion, regardless of symptoms or EKG findings; and digoxin level of more than 10 ng/mL or the ingestion of more than 10 mg of digoxin, regardless of symptoms or EKG findings. Digibind is an antibody that binds to digoxin in the plasma and interstitial space, creating a concentration gradient for the exit of intracellular digoxin. As poisoning of the Na+-K+ ATPase is relieved and K+ is pumped intracellularly with the potential of causing hypokalemia, the potassium levels should be monitored when Digibind is used. The half-life of the digoxin-Digibind complex is 15 to 20 hours if renal function is normal. Serum digoxin concentration rises significantly after Digibind use (as tissue digoxin is released into the bloodstream bound to the antibody) and should not be measured.

25. What four classes of drugs exacerbate the syndrome of heart failure and should be avoided in most heart failure with reduced ejection fraction patients?

- Antiarrhythmic agents as a class are generally contraindicated in patients with HFrEF. Most can exert cardiodepressant and proarrhythmic effects. Only amiodarone and dofetilide appear to have a neutral effect on survival.
- Calcium channel blockers, more specifically the nondihydropyridine group, can lead to worsening heart failure and have been associated with an increased risk of cardiovascular events. Only the dihydropyridines or vasoselective calcium channel blockers have been shown not to adversely affect survival and can be used in select patients needing improved blood pressure control.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause sodium retention and peripheral vasoconstriction by directly inhibiting sodium resorption in the ascending loop of Henle and distal collecting ducts. This can attenuate the efficacy and enhance the toxicity of diuretics and ACE inhibitors.
- Thiazolidinediones were developed to increase insulin sensitivity by activating peroxisome proliferator-activated receptors (PPARs), which forces cells to increase reliance on oxidation of carbohydrates rather than fatty acids. However, these medications also have effects on the renal tubules, where PPARs act to direct sodium resorption in the collecting ducts. They can lead to sodium retention and onset of heart failure symptoms in those without a history of heart failure

26. Is dietary restriction of sodium recommended in patients with symptomatic heart failure?

Yes. In general, patients should restrict themselves to 2 to 3 g sodium daily and less than 2 g daily in moderate to severe cases of heart failure.

27. Is fluid restriction recommended in all patients with heart failure?

Not necessarily. Fluid restriction is generally reserved for those patients with advanced or Stage D heart failure

Fluid restriction is recommended for patients with

(1) hyponatremia (sodium less than 130 mEq/L) or

(2) fluid retention difficult to control despite high doses of diuretics and sodium restriction. In such cases, patients are generally restricted to less than 2 L/day.

28. Should patients with heart failure be told to use salt substitutes instead of salt?

In some cases, the answer is no. Many salt substitutes contain potassium chloride in place of sodium chloride. This could lead to potential hyperkalemia in patients on potassium-sparing diuretics, ACE inhibitors or ARBs, aldosterone antagonists, and in those with chronic kidney disease (or those with the potential to develop acute renal failure). Patients who are permitted to use salt substitutes need to be cautioned about potassium issues.

29. What are the current criteria for consideration of cardiac resynchronization therapy with biventricular pacing?

The 2012 ACC/AHA/Heart Rhythm Society (HRS) guidelines on device-based therapy updated their recommendations for those who should receive CRT (with a class I indication) with or without ICD. The recommendation expanded to include those with NYHA class II heart failure symptoms. However, in the CRT for Mild to Moderate Heart Failure Study published in 2010 by the RAFT investigators, there was also a new finding that those who benefit from resynchronization predominantly have a QRS greater than 150 ms. Therefore current class I recommended criteria for CRT include

- Presence of sinus rhythm
- Class II, III, or ambulatory class IV symptoms despite good medical therapy
- LVEF less than or equal to 35%
- QRS more than 150 ms (especially if left bundle branch block morphology is present) CRT may also be considered in those with less prolonged QRS duration (120 to 150 ms), although benefit is generally not as great and/or not as well established.

30. Which patients with heart failure should be considered for an implantable cardioverter defibrillator?

ICD should only be considered in patients with a reasonable expectation of survival with an acceptable functional status for at least 1 year. Class I recommendations for ICD include the following:

- Secondary prevention (cardiac arrest survivors of VT/ventricular fibrillation [VF], hemodynamically unstable sustained VT)
- Structural heart disease and sustained VT, whether hemodynamically stable or unstable
- Syncope of undetermined origin with hemodynamically significant sustained VT or VF induced at electrophysiologic study
- LVEF less than or equal to 35% at least 40 days after MI and NYHA functional class II and III
- LVEF less than 30% at least 40 days after MI and NYHA functional class I
- LVEF less than or equal to 35% despite medical therapy in patient with nonischemic cardiomyopathy and NYHA functional class II and III
- Nonsustained VT caused by prior MI, LVEF less than 40%, and inducible VF or sustained VT at electrophysiologic study

31. How is advanced heart failure defined?

Advanced heart failure is recognized when heart failure patients follow the below clinical patterns:

- More than two hospitalizations or emergency room visits in the past 1 year for heart failure symptoms
- Progressive decline in renal function
- Progressive weight loss without other identifiable cause, known as cardiac cachexia
- Intolerance to beta-blockers due to worsening heart failure or hypotension
- Frequent systolic blood pressure less than 90 mm Hg
- Frequent dyspnea during dressing or bathing requiring rest
- Inability to walk one block on level ground due to dyspnea or fatigue
- Progressive decline in serum sodium, usually less than 133 mEq/L
- Frequent ICD shocks
- Need to escalate diuretic therapy to maintain volume status, usually reaching an equivalent daily dose of greater than 160 mg furosemide/day and/or need for daily supplemental metolazone therapy

- *Thanks alot*