

CARDIOLOGY II

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Learning Objectives

1. Recommend patient-specific pharmacologic therapy for the management of chronic heart failure, with an emphasis on mortality-reducing agents and their target doses.
2. Develop an evidence-based pharmacologic regimen and monitoring plan for patients with atrial fibrillation.
3. Develop an optimal pharmacologic management plan for a patient with hypertension according to practice guidelines and clinical trial evidence.
4. Identify patients at risk of atherosclerotic cardiovascular disease (ASCVD) according to the pooled cohort equation to estimate the 10-year ASCVD risk and determine in whom statin therapy should be initiated.
5. In patients with or at risk of ASCVD, determine the appropriate intensity of statin therapy according to the four identified benefit groups.

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. R.S., a 58-year-old woman with a history of hypertension (HTN), coronary heart disease (CHD), myocardial infarction (MI) 4 months ago, and dyslipidemia, presents to the clinic for follow-up. She is without complaints and has no worsening signs or symptoms of dyspnea or edema compared with her baseline. An echocardiogram reveals a left ventricular ejection fraction (LVEF) of 35%. She is in New York Heart Association (NYHA) class III. Her medications include aspirin 81 mg/day, metoprolol succinate 150 mg/day, and simvastatin 20 mg every night. Her vital signs include heart rate (HR) 58 beats/minute and blood pressure (BP) 138/80 mm Hg. Her lungs are clear, and laboratory results are within normal limits. Given her history and physical examination, which is the most appropriate modification to R.S.'s current drug therapy?
 - A. Continue current therapy.
 - B. Initiate digoxin 0.125 mg/day.
 - C. Initiate spironolactone 25 mg/day.
 - D. Initiate lisinopril 5 mg/day.
2. J.O. is a 64-year-old woman with NYHA class II nonischemic dilated cardiomyopathy (LVEF of 30%). She presents to the heart failure (HF) clinic for follow-up. She has no complaints. Her medications include enalapril 10 mg twice daily, furosemide 40 mg twice daily, and potassium chloride 20 mEq twice daily. Her vital signs include BP 130/88 mm Hg and HR 78 beats/minute. Her laboratory results are within normal limits. Which would be the best option to further manage J.O.'s HF?
 - A. Continue current regimen.
 - B. Increase enalapril to 20 mg twice daily.
 - C. Initiate carvedilol 3.125 mg twice daily.
 - D. Initiate digoxin 0.125 mg/day.
3. J.M. is a 65-year-old woman with a history of HTN and poor medication adherence who presents to her primary care physician with shortness of breath and markedly decreased exercise tolerance. An echocardiogram reveals an LVEF of 65%, with diastolic dysfunction. J.M.'s medications include extended-release nifedipine 90 mg/day and hydrochlorothiazide 25 mg/day. Her vital signs include BP 128/78 mm Hg and HR 98 beats/minute. Her lung fields are clear to auscultation, and there is no evidence of systemic congestion. Which is the best pharmacologic management for J.M.?
 - A. Discontinue extended-release nifedipine and initiate diltiazem 240 mg/day.
 - B. Discontinue hydrochlorothiazide and initiate furosemide 40 mg twice daily.
 - C. Initiate digoxin 0.125 mg/day.
 - D. Add lisinopril 5 mg/day.
4. B.W. is a 78-year-old man with a history of HTN, peripheral arterial disease (PAD), gastroesophageal reflux disease, and atrial fibrillation (AF) for the past month. His therapy includes aspirin 325 mg/day, lansoprazole 30 mg every night, atenolol 50 mg/day, lisinopril 10 mg/day, and atorvastatin 20 mg/day. His vital signs include BP 132/72 mm Hg and HR 68 beats/minute. Which is the best therapy for B.W. at this time?
 - A. Add diltiazem and warfarin.
 - B. Add digoxin and increase lisinopril to 20 mg/day.

- C. Discontinue atorvastatin and add warfarin.
- D. Add warfarin and decrease aspirin to 81 mg/day.
5. Z.G. is a 61-year-old man with AF, HTN, and hypercholesterolemia. His medications include digoxin 0.125 mg/day, warfarin 5 mg/day, amlodipine 10 mg/day, and pravastatin 20 mg every night. He comes to the clinic today with no complaints except for palpitations and shortness of breath when doing yard work. His vital signs include BP 138/80 mm Hg and HR 100 beats/minute. All laboratory results are within normal limits; his international normalized ratio (INR) is 2.4, and his digoxin concentration is 1.1 ng/dL. Which is the best option to help with Z.G.'s symptoms?
- A. Add metoprolol succinate 50 mg/day.
- B. Increase digoxin to 0.25 mg/day.
- C. Continue current regimen; advise the patient to avoid activities that cause symptoms.
- D. Add verapamil 240 mg/day.
6. R.P. is an 82-year-old African American man with a history of HTN, transient ischemic attack (TIA), and gout. His medications include allopurinol 300 mg/day, amlodipine 10 mg/day, lisinopril 40 mg/day, and aspirin 81 mg/day. His vital signs include BP 145/85 mm Hg and HR 82 beats/minute. Which is the best approach to improve R.P.'s BP control?
- A. Add hydrochlorothiazide 25 mg/day to achieve a systolic BP goal of less than 150 mm Hg.
- B. Increase lisinopril to 80 mg/day and titrate to achieve a systolic BP goal of less than 130 mm Hg.
- C. Add atenolol 50 mg/day to achieve a systolic BP less than 140 mm Hg.
- D. Make no changes to his current medications because his systolic BP is at goal.
7. J.T. is a 58-year-old man who presents to his primary care provider for the first time in 10 years. He has smoked 2 packs/day for the past 30 years and takes no medication. A fasting lipid panel shows total cholesterol (TC) 222 mg/dL, low-density lipoprotein cholesterol (LDL-C) 105 mg/dL, triglycerides (TG) 330 mg/dL, and high-density lipoprotein cholesterol (HDL-C) 51 mg/dL. His vital signs include BP 140/75 mm Hg and HR 80 beats/minute. His pooled cohort equation reveals a 10-year ASCVD risk of 14.6%. According to his risk, which would be the best pharmacologic therapy to initiate in J.T.?
- A. Initiate simvastatin 20 mg once daily and gemfibrozil 600 mg twice daily.
- B. Initiate rosuvastatin 5 mg once daily.
- C. Initiate pravastatin 20 mg once daily and fenofibrate 160 mg once daily.
- D. Initiate atorvastatin 40 mg once daily.
8. J.S. is a 43-year-old man with HTN who presents for an annual physical. His family history is significant for his father having CHD. His only medication is lisinopril 10 mg once daily. His BP is 145/90 mm Hg. A fasting lipid profile is obtained that reveals TC 238 mg/dL, TG 95 mg/dL, LDL-C 176 mg/dL, and HDL-C 43 mg/dL. His calculated 10-year risk according to the pooled cohort equation is 3.9%. According to his history and calculated 10-year risk, which best describes the next step for management in J.S.?
- A. Initiate high-intensity statin therapy.
- B. Do not initiate statin therapy and reevaluate risk in 1–3 years.
- C. Initiate moderate-intensity statin therapy.
- D. Do not initiate statin therapy and reevaluate risk in 4–6 years.
9. J.C. is a 62-year-old man (weight 135 kg [1 month ago 143 kg], height 178 cm) with a history of diabetes, chronic renal insufficiency, bipolar disorder, CHD, and hypertriglyceridemia that, in the past, has resulted in pancreatitis. His family history is significant for his father having CHD and hypertriglyceridemia. He is not a smoker but admits drinking a 6-pack of beer daily. Pertinent laboratory findings include a hemoglobin A1C of 11.6% and a serum creatinine of 2.6 mg/dL. He currently takes atorvastatin 40 mg every evening, aspirin 81 mg/day, metformin 1000 mg twice daily, olanzapine 10 mg/day, metoprolol tartrate 50 mg twice daily, and coenzyme Q10 200 mg/day. His fasting

lipid profile is TC 402 mg/dL, LDL-C unable to calculate, HDL-C 48 mg/dL, and TG 1500 mg/dL. Which best describes potential secondary causes of elevated TGs that should be considered in J.C.?

- A. Obesity, poorly controlled diabetes, olanzapine, metoprolol, coenzyme Q10.
- B. Alcohol consumption, poorly controlled diabetes, weight loss, β -blockers.
- C. Obesity, alcohol consumption, β -blockers, olanzapine, biliary obstruction.
- D. Alcohol consumption, obesity, poorly controlled diabetes, olanzapine, metoprolol.

Patient Cases

1. L.S. is a 48-year-old woman with alcohol-induced cardiomyopathy. Her most recent left-ventricular ejection fraction (LVEF) is 20%; her daily activities are limited by dyspnea and fatigue (New York Heart Association [NYHA] class III). Her medications include lisinopril 20 mg/day, furosemide 40 mg twice daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day. She has been stable on these doses for the past month. Her most recent laboratory results include: sodium (Na) 140 mEq/L, potassium (K) 4.0 mEq/L, chloride 105 mEq/L, bicarbonate 26 mEq/L, blood urea nitrogen (BUN) 12 mg/dL, serum creatinine (SCr) 0.8 mg/dL, glucose 98 mg/dL, calcium 9.0 mg/dL, phosphorus 2.8 mg/dL, magnesium (Mg) 2.0 mEq/L, and digoxin 0.7 ng/mL. Her vital signs today include blood pressure (BP) 112/70 mm Hg and heart rate (HR) 68 beats/minute. Which is the best approach for maximizing the management of her heart failure (HF)?
 - A. Increase carvedilol to 25 mg twice daily.
 - B. Increase lisinopril to 40 mg/day.
 - C. Increase spironolactone to 50 mg/day.
 - D. Increase digoxin to 0.25 mg/day.

2. J.T. is a 62-year-old man with a history of coronary heart disease (CHD) (myocardial infarction [MI] 3 years ago), hypertension [HTN], depression, chronic renal insufficiency (baseline SCr 2.8 mg/dL), peripheral arterial disease (PAD), osteoarthritis, hypothyroidism, and HF (LVEF of 25%). His medications include aspirin 81 mg/day, simvastatin 40 mg every night, enalapril 5 mg twice daily, metoprolol succinate 50 mg/day, furosemide 80 mg twice daily, cilostazol 100 mg twice daily, acetaminophen 650 mg four times daily, sertraline 100 mg/day, and levothyroxine 0.1 mg/day. His vital signs include; BP 120/70 mm Hg and HR 72 beats/minute. Pertinent laboratory results include K 4.1 mEq/L, SCr 2.8 mg/dL, and a thyroid-stimulating hormone of 2.6 mIU/L. His HF is stable and considered NYHA class II. Which is the best approach for maximizing the management of his HF?
 - A. Discontinue metoprolol and begin carvedilol 12.5 mg twice daily.
 - B. Increase enalapril to 10 mg twice daily.
 - C. Add spironolactone 25 mg/day.
 - D. Add digoxin 0.125 mg/day.

I. HEART FAILURE

- A. Background: Heart failure is a complex clinical syndrome caused by any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
 1. HF with reduced ejection fraction (HF_rEF) or systolic dysfunction
 - a. Defined as a clinical diagnosis of HF and an LVEF of 40% or less
 - b. Dilated ventricle
 - c. Two-thirds of cases are attributable to CHD.
 - d. One-third of cases are attributable to nonischemic cardiomyopathy.
 - i. Hypertension
 - ii. Thyroid disease
 - iii. Obesity
 - iv. Stress (Takotsubo)

- v. Cardiotoxins
 - (a) Alcohol
 - (b) Chemotherapeutic agents
 - (1) Anthracyclines
 - (2) Cyclophosphamide (high dose)
 - (3) Fluorouracil
 - (4) Trastuzumab
 - (c) Cocaine
 - vi. Myocarditis
 - vii. Idiopathic
 - viii. Tachycardia
 - ix. Peripartum
2. Heart failure with preserved EF (HFpEF) or diastolic dysfunction
 - a. Defined as an LVEF of 50% or greater; HFpEF borderline EF 41%–49%
 - b. Accounts for about 30% (highly variable) of patients with HF
 - c. Impaired ventricular relaxation and filling
 - d. Normal wall motion
 - e. Most common cause is HTN (60%–89%).
 3. Primary symptoms
 - a. Dyspnea
 - b. Fatigue
 - c. Edema
 - d. Exercise intolerance
 4. Stages and functional class of HF according to the American College of Cardiology/American Heart Association (ACC/AHA) (Table 1)

Table 1. HF Failure Stages and Corresponding NYHA Functional Class

Stage		NYHA Functional Class	
A	At high risk of HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	Asymptomatic HF. No limitations in physical activity caused by HF symptoms
C	Structural heart disease with prior or current symptoms of HF	I	No limitations in physical activity caused by HF symptoms
		II	Slight limitation of physical activity. Asymptomatic at rest but symptoms of HF with normal level of activity
		III	Marked limitations in physical activity because of HF symptoms. Asymptomatic at rest.
		IV	Symptoms of HF at rest or unable to carry out any physical activity
D	Refractory HF requiring specialized interventions	IV	Symptoms of HF at rest

HF = heart failure; MI = myocardial infarction; NYHA = New York Heart Association.

Adapted from 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. *J Am Coll Cardiol* 2013;62:e147-239.

5. Goals of therapy
 - a. Modify or control risk factors (e.g., HTN, obesity, diabetes).
 - b. Manage structural heart disease.
 - c. Reduce morbidity and mortality.
 - d. Prevent or minimize Na and water retention.
 - e. Eliminate or minimize HF symptoms.
 - f. Block compensatory neurohormonal activation caused by reduced cardiac output (CO).
 - g. Slow progression of worsening cardiac function.

- B. HFrEF or Systolic Failure
 1. Pharmacologic therapy
 - a. Diuretics
 - i. Place in therapy: Indicated in patients with evidence of fluid retention (class I indication)
 - ii. Short-term benefit (days)
 - (a) Decreased jugular venous distension
 - (b) Decreased pulmonary congestion
 - (c) Decreased peripheral edema
 - iii. Intermediate-term benefits (weeks to months)
 - (a) Decreased daily symptoms
 - (b) Increased exercise tolerance
 - iv. Long-term benefits (months to years): No benefit on mortality
 - v. Mechanism of action: Inhibits reabsorption of Na in the ascending limb of the loop of Henle (loops) or in the distal tubule (thiazides)
 - vi. Dosing and administration considerations
 - (a) Should generally be combined with an angiotensin-converting enzyme (ACE) inhibitor, β -blocker, and aldosterone antagonist
 - (b) Start with a low initial dose; may then double the dose and titrate according to the patient's weight and diuresis. Note that differences exist in the bioavailability of oral doses.
 - (c) If a patient has fluid overload, initiate and adjust therapy to result in 1–2 lb of weight loss per day (may be more aggressive in the inpatient setting).
 - (d) Chronic therapy should be adjusted to maintain a euolemic state.
 - (e) May combine with another diuretic class (e.g., thiazide diuretic) for synergy, if needed
 - (f) Loop diuretics are preferred because of their greater diuretic capabilities; loop diuretics also retain efficacy with decreased renal function.
 - vii. Monitoring: Monitor and replace K and Mg as needed, especially with loop diuretics (goal with cardiovascular [CV] disease is K of 4.0 mEq/L or greater and Mg of 2.0 mEq/L or greater to minimize the risk of arrhythmias).

Table 2. Diuretics and Recommended Dosing^a

Agent	Oral Bioavailability (%)	Initial Daily Dose	Maximal Total Daily Dose (mg)	Duration of Action (hr)
Loop Diuretics (inhibit 20%–25% of sodium reabsorption)				
Furosemide ^b	10–67	20–40 mg once or twice daily	600	6–8
Bumetanide ^b	80–100	0.5–1 mg once or twice daily	10	4–6
Torsemide ^b	80–100	10–20 mg daily	200	12–16
Ethacrynic acid ^b	100	25–50 mg once or twice daily	200	
Thiazide Diuretics (inhibit 10%–15% of sodium reabsorption)				
Hydrochlorothiazide	65–75	25 mg once or twice daily	100	6–12
Metolazone	40–65	2.5 mg daily	20	12–24
Chlorthalidone	64	12.5–25 mg daily	100	24–72
Chlorothiazide ^b	30–50	250–500 once or twice daily	2000	6–12

^aEquivalent doses: furosemide 40 mg = bumetanide 1 mg = torsemide 10–20 mg = ethacrynic acid 50 mg.

^bAvailable in oral and intravenous formulations.

- b. ACE inhibitors (class I indication)
 - i. Place in therapy: Recommended in all patients with HFrEF and current or prior symptoms, unless contraindicated
 - ii. Benefits
 - (a) Decreased mortality (about 25%–50% relative risk reduction compared to placebo depending on severity of HF)
 - (b) Decreased hospitalizations (about 30% relative risk reduction compared to placebo)
 - (c) Symptom improvement
 - (d) Improved clinical status
 - (e) Improved sense of well-being
 - iii. Mechanism of action
 - (a) Blocks production of angiotensin II
 - (1) Decreases sympathetic stimulation
 - (2) Decreases production of aldosterone and vasopressin
 - (3) Decreases vasoconstriction (afterload and preload)
 - (b) Increases bradykinins (decreases their metabolism)
 - (1) Increases vasodilatory prostaglandins
 - (2) May affect myocardial remodeling
 - iv. Dosing and administration considerations
 - (a) Start low and double the dose every 1–4 weeks to target dose (Table 3).
 - (b) Compared with patients with systolic dysfunction who received low-dose lisinopril (2.5–5 mg/day), patients who received high-dose lisinopril (32.5–35 mg/day) had no difference in all-cause mortality or CV mortality but did have a significant 12% lower risk of death or hospitalization for any reason and 24% fewer hospitalizations for HF.
 - (c) Patient may notice improvement in symptoms in several weeks.

- (d) Avoid use in patients who have experienced angioedema or those who are pregnant or plan to become pregnant.
- (e) Use caution if systolic BP is less than 80 mm Hg, SCr is greater than 3 mg/dL, or elevated K is greater than 5.0 mEq/L or in bilateral renal artery stenosis.
- v. Monitoring
 - (a) SCr and K 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (preexisting hypotension, diabetes, K supplements, azotemia)
 - (1) SCr may rise (up to a 20% increase is acceptable) because of renal efferent artery dilation (results in a slightly decreased glomerular filtration rate). Rarely, acute renal failure occurs, especially if the patient is intravascularly depleted (be careful to avoid overdiuresis).
 - (2) Monitor BP and symptoms of hypotension (e.g., dizziness, light-headedness).
 - (A) BP may be low to begin with because of low CO.
 - (B) $BP = \text{cardiac output (CO)} \times \text{systemic vascular resistance (SVR)}$.
 - (C) In HF, as CO increases because of decreased SVR, BP may decrease slightly or remain the same.
 - (D) Symptoms of hypotension are often not present with small dose increases. Remember to treat the patient, not the number.
 - (3) Ninety percent of people tolerate ACE inhibitors.
 - (A) Angioedema (less than 1%): May switch to angiotensin II receptor blockers (ARBs; cross-reactivity is 2.5%) or hydralazine–isosorbide dinitrate
 - (B) Cough (20%): May switch to ARBs (less than 1%)

Table 3. ACE Inhibitors and Recommended Dosing

Drug	Starting Dosage	Target Dosage	Maximal Dosage
Captopril	6.25 mg TID	50 mg TID	50 mg TID
Enalapril	2.5 mg BID	10 mg BID	20 mg BID
Lisinopril	2.5–5 mg/day	20 mg/day	40 mg/day
Perindopril	2 mg/day	8 mg/day	16 mg/day
Ramipril	1.25–2.5 mg/day	10 mg/day	10 mg/day
Trandolapril	1 mg/day	4 mg/day	4 mg/day

Note: Fosinopril and quinapril may be used; however, they do not have the same magnitude of mortality-reducing data as listed above. ACE = angiotensin-converting enzyme; BID = twice daily; TID = three times daily.

- c. Angiotensin receptor blockers (ARBs): Place in therapy
 - i. Recommended in patients with HFrEF with current or prior symptoms who are unable to take an ACE inhibitor
 - ii. Have not been proven superior to ACE inhibitors at target HF dosages
 - iii. Reasonable alternative to ACE inhibitors as first-line therapy if the patient is already taking an ARB or as substitute for an ACE inhibitor in patients unable to take ACE inhibitors because of cough (class I indication)
 - iv. May be considered in addition to an ACE inhibitor if persistently symptomatic and already taking an ACE inhibitor and a β -blocker but only when an aldosterone antagonist is not tolerated or indicated (class IIb recommendation)
 - v. Possibly considered if patient has experienced ACE inhibitor–induced angioedema
 - vi. Do not combine with an ACE inhibitor and an aldosterone antagonist because this may be harmful.

Table 4. ARBs and Recommended Dosing

Drug	Starting Dosage	Target Dosage
Candesartan	4–8 mg/day	32 mg/day
Losartan	25–50 mg/day	150 mg/day
Valsartan	20–40 mg BID	160 mg BID

ARB = angiotensin receptor blocker; BID = twice daily.

- d. β -Blockers
- i. Place in therapy
 - (a) Recommended in all patients with HF \neq EF with current or prior symptoms unless contraindicated (class I indication)
 - (b) Benefits of β -blockade (when added to an ACE inhibitor)
 - (1) Decreased mortality (about 35% relative risk reduction compared with placebo)
 - (2) Decreased hospitalizations (about 25% relative risk reduction compared with placebo)
 - (3) Symptom improvement
 - (4) Improved clinical status
 - (5) Produce greater symptom improvement and reduction in the risk of death at higher doses than ACE inhibitors
 - ii. Mechanism of action
 - (a) Blocks the effect of norepinephrine and other sympathetic neurotransmitters on the heart and vascular system
 - (1) Decreases ventricular arrhythmias (sudden cardiac death)
 - (2) Decreases cardiac hypertrophy and cardiac cell death
 - (3) Decreases vasoconstriction and HR
 - (b) Carvedilol also provides α_1 -blockade.
 - (1) Further decreases SVR (afterload)
 - (2) Results in greater reduction in BP than metoprolol succinate
 - iii. Dosing and administration considerations
 - (a) Only bisoprolol, carvedilol, and metoprolol succinate are recommended in HF \neq EF.
 - (b) Add to existing ACE inhibitor therapy (at least at a low dose) when HF symptoms are stable and patients are euvolemic.
 - (c) Should not be prescribed without diuretics in patients with current or recent history of fluid retention
 - (d) Start low and increase (double) the dose every 2 weeks (or slower, if needed) to target dose. Aim to achieve target dose in 8–12 weeks (Table 5).
 - (e) Avoid abrupt discontinuation; can precipitate clinical deterioration
 - (f) May not notice improvement in symptoms for several months
 - (g) Should be considered even in patients with reactive airway disease or asymptomatic bradycardia
 - iv. Monitoring
 - (a) BP, HR, and symptoms of hypotension (monitor in 1–2 weeks)
 - (1) Significant hypotension, bradycardia, or dizziness occurs in about 1% of patients on β -blocker therapy when the β -blocker is titrated slowly. If these symptoms appear, lower the dose by 50%.
 - (2) Of importance, remember that higher β -blocker doses are associated with greater mortality reduction. Therefore, if hypotension alone is the problem, try reducing the ACE inhibitor (or another antihypertensive) first.

- (b) Increased edema or fluid retention (monitor in 1–2 weeks)
 - (1) From 1% to 2% more common than with placebo (in euvolemic, stable patients)
 - (2) Responds to diuretic increase
- (c) Fatigue or weakness
 - (1) From 1% to 2% more common than with placebo
 - (2) Usually resolves spontaneously in several weeks
 - (3) May require dosage decrease or discontinuation

Table 5. β -Blockers and Recommended Dosing

Agent	Starting Dosage	Target Dosage
Bisoprolol	1.25 mg/day	10 mg/day
Carvedilol	3.125 mg BID	25 mg BID ^a
Carvedilol CR	10 mg/day	80 mg/day
Metoprolol succinate XL ^b (metoprolol CR/XL)	12.5–25 mg/day	200 mg/day

^a50 mg twice daily if weight is more than 85 kg.

^bLittle or no data exists for metoprolol tartrate.

BID = twice daily; CR = controlled release; XL = extended release.

- e. Aldosterone receptor antagonists
 - i. Place in therapy
 - (a) Recommended in NYHA class II–IV patients with an LVEF of 35% or less to reduce morbidity and mortality unless a contraindication exists. Patients with NYHA class II should have a history of CV hospitalization or elevated brain natriuretic peptide (BNP) levels (class I indication).
 - (b) Recommended to reduce morbidity and mortality in patients after a (MI) when they have an LVEF less than 40% with symptoms of HF or an LVEF less than 40% and diabetes (class I indication)
 - ii. Benefits of spironolactone in NYHA class III and IV HF
 - (a) Decreased all-cause mortality (30% relative risk reduction compared to placebo)
 - (b) Decreased hospitalizations for HF (35% relative risk reduction compared to placebo)
 - (c) Improved symptoms
 - iii. Benefits of eplerenone (selective aldosterone antagonist) in NYHA class II HF
 - (a) Decreased death from CV causes or hospitalization from HF (37% relative risk reduction compared to placebo)
 - (b) Decreased hospitalizations from HF (42% relative risk reduction compared with placebo)
 - (c) Decreased mortality (24% relative risk reduction compared to placebo)
 - iv. Benefits of eplerenone in LV dysfunction after MI
 - (a) Decreased mortality (15% relative risk reduction compared to placebo)
 - (b) Decreased the composite of death from CV causes or hospitalization for CV events (13% relative reduction compared to placebo)
 - v. Mechanism of action: Blocks effects of aldosterone in the kidneys, heart, and vasculature
 - (a) Decreases K and Mg loss; decreases ventricular arrhythmias
 - (b) Decreases Na retention; decreases fluid retention
 - (c) Eliminates catecholamine potentiation; decreases BP
 - (d) Blocks direct fibrotic actions on the myocardium

- vi. Dosing and administration considerations
 - (a) Should be added to ACE inhibitor (or ARB) and β -blocker therapy
 - (b) SCr should be less than 2.5 mg/dL for men and less than 2.0 mg/dL in women, and K should be less than 5.0 mEq/L (Table 6).
 - (1) Avoid use if SCr is greater than 2.5 mg/dL, creatinine clearance (CrCl) is less than 30 mL/minute, or K is greater than 5.0 mEq/L.
 - (2) In the absence of hypokalemia (K less than 4.0 mEq/L), supplemental K is not recommended when taking an aldosterone antagonist.

Table 6. Dosing of Aldosterone Antagonists

Parameters	Eplerenone	Spironolactone
Estimated CrCl >50 mL/minute and K \leq 5 mEq/L	25 mg once daily	12.5–25 mg once daily
Maintenance dose after 1 month if K \leq 5 mEq/L and CrCl > 50 mL/minute	50 mg once daily	25 mg once or twice daily
Estimated CrCl 30–40 mL/minute	25 mg every other day	12.5 mg once daily or every other day
Maintenance dose after 1 month if K \leq 5 mEq/L and CrCl > 30–49 mL/minute	25 mg once daily	12.5–25 mg once daily

- vii. Monitoring
 - (a) K and SCr within 2–3 days and again at 7 days after starting therapy, then monthly for first 3 months, then every 3 months thereafter. If the dose of ACE inhibitor or ARB is increased, restart monitoring.
 - (1) Hyperkalemia was reported in only 2% of the patients in the trial; however, in practice, it occurs in about 20% of patients.
 - (2) Decrease dose by 50% or discontinue if K is greater than 5.5 mEq/L.
 - (b) Gynecomastia
 - (1) Spironolactone is reported at a rate of 10% in clinical trials.
 - (2) Eplerenone may be considered an alternative to spironolactone in painful gynecomastia.
- f. Digoxin
 - i. Place in therapy: Can be beneficial in decreasing hospitalizations in patients with HFrEF (class IIa indication)
 - ii. Benefits
 - (a) Improved symptoms
 - (b) Improved exercise tolerance
 - (c) Decreased hospitalizations
 - (d) No effect on mortality
 - iii. Mechanism of action (in HF): Inhibits Na-K ATP
 - (a) Decreases central sympathetic outflow by sensitizing cardiac baroreceptors
 - (b) Decreases renal reabsorption of Na
 - (c) Minimal increase in cardiac contractility because of the inhibition of Na-K ATP
 - iv. Dosing and administration considerations
 - (a) SCr should be monitored because the drug is cleared more than 95% renally.
 - (b) For most patients, 0.125 mg/day is adequate to achieve the desired serum concentration.
 - (c) Consider dosing 0.125 mg every other day in patients older than 70 years, those with impaired renal function, or those with low lean body mass.
 - (d) No indication to load patients with digoxin in the setting of HF

- (e) Drug interactions: Digoxin concentrations are increased with concomitant:
 - (1) Clarithromycin, erythromycin
 - (2) Amiodarone, dronedarone
 - (3) Itraconazole, posaconazole, voriconazole
 - (4) Cyclosporine, tacrolimus
 - (5) Verapamil
- v. Monitoring: Serum concentrations should be less than 1 ng/mL; in general, concentrations of 0.5–0.9 ng/mL are suggested.
 - (a) Minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations
 - (b) Risk of toxicity increases with age and renal dysfunction.
 - (c) Risk of toxicity increases in the presence of hypokalemia, hypomagnesemia, or hypercalcemia.
 - (d) Signs of toxicity generally include nausea, vomiting, vision changes.
 - (e) SrCr should be monitored due to high dependence on renal function for clearance.
- g. Hydralazine/isosorbide dinitrate
 - i. Place in therapy
 - (a) Recommended in addition to ACE inhibitors and β -blockers to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III or IV HFrEF (class I indication)
 - (b) May be useful in patients with current or prior symptoms of HFrEF who are unable to tolerate an ACE inhibitor or an ARB (class IIa indication)
 - ii. Benefits
 - (a) Decreased mortality (43% relative risk compared to placebo)
 - (b) Decreased hospitalizations (39% relative risk compared to placebo)
 - iii. Mechanism of action
 - (a) Hydralazine
 - (1) Arterial vasodilator (reduces afterload)
 - (2) Increases effect of nitrates through antioxidant mechanisms
 - (b) Isosorbide dinitrate
 - (1) Stimulates nitric acid signaling in the endothelium
 - (2) Effective in reducing preload
 - iv. Dosing and administration considerations
 - (a) Hydralazine (25–75 mg three or four times daily); isosorbide dinitrate (10–40 mg three times daily)
 - (b) Fixed-dose BiDil (hydralazine 37.5 mg plus isosorbide dinitrate 20 mg) with a goal dose of 2 tablets three times daily
 - v. Monitoring
 - (a) Headache
 - (b) Hypotension
 - (c) Drug-induced lupus with hydralazine
- h. Other medication therapies
 - i. Anticoagulation
 - (a) Recommended in HF with permanent, persistent, paroxysmal atrial fibrillation (AF) with an additional risk factor for stroke (no preference on agent)
 - (b) Reasonable in patients with HF who have permanent, persistent, paroxysmal AF without an additional risk factor for stroke
 - (c) Not recommended in the absence of AF, prior stroke, or a cardioembolic source

- ii. Statins: Not recommended solely on the basis of HF diagnosis
- iii. Omega-3 fatty acids: Reasonable adjunctive therapy in NYHA class II–IV symptoms and HFrEF or HFpEF (class IIa recommendation)
- iv. Antiarrhythmics: Amiodarone and dofetilide are the preferred antiarrhythmics that should be used in HFrEF for patients with arrhythmias given neutral effects on mortality.
- v. Calcium channel blockers: Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful and should be avoided.
- i. Device therapy
 - i. Implantable cardioverter defibrillator (ICD): Recommended for primary prevention of sudden cardiac death in ischemic and nonischemic patients
 - (a) Qualifying criteria include 40 days post-MI, LVEF of 35% or less, or NYHA class II or III symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year (class I indication).
 - (b) Patients 40 days post-MI, LVEF of 30% or less, and NYHA class I symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year.
 - ii. Chronic resynchronization therapy: Recommended for those with an LVEF of 35% or less, in sinus rhythm, and a left bundle branch block with a QRS of 150 milliseconds or greater on optimal medical therapy with NYHA class II–III symptoms or NYHA class IV with ambulation
- 2. Nonpharmacologic therapy for HFrEF
 - a. Prevent further cardiac injury.
 - i. Discontinue smoking.
 - ii. Reduce weight if obese.
 - iii. Control HTN.
 - iv. Control diabetes mellitus.
 - v. Decrease alcohol to 2 or fewer drinks a day for men and 1 or fewer drinks a day for women.
 - vi. Eliminate alcohol if cardiomyopathy is alcohol induced.
 - vii. Limit Na intake to 1500 mg/day for stages A and B consider less than 3 g/day for stages C and D.
 - b. Restricting fluid intake to 1.5–2 L/day is reasonable in stage D if serum Na is low.
 - c. Modest exercise program benefits
 - i. Possible modest effects on all-cause hospitalization and all-cause mortality, CV death or CV hospitalization, and CV death or HF hospitalization
 - ii. Safe for patients with HF
 - d. Annual influenza vaccine and pneumococcal vaccine every 5 years
 - e. Monitor and appropriately replace electrolytes (minimize risk of arrhythmias).
 - f. Monitor for thyroid disease.
 - i. Hypothyroidism may be masked by HF symptoms.
 - ii. Hyperthyroidism will worsen systolic dysfunction.
 - g. Screen for and treat depression.

Patient Case

3. Which of J.T.'s (from Patient Case 2) drugs is most likely to adversely affect his cardiac prognosis?
- A. Acetaminophen.
 - B. Sertraline.
 - C. Cilostazol.
 - D. Levothyroxine.

3. Drugs to avoid or use with caution in HF_rEF
- a. Nonsteroidal anti-inflammatory drugs (NSAIDs, including selective cyclooxygenase-2 inhibitors)
 - i. Promote Na and water retention
 - ii. Blunt diuretic response
 - iii. Increase morbidity and mortality
 - b. Corticosteroids: Promote Na and water retention
 - c. Class I and III antiarrhythmic agents (except for amiodarone and dofetilide)
 - i. Negative inotropic activity
 - ii. Proarrhythmic effects
 - iii. Amiodarone and dofetilide have been proven safe in patients with HF.
 - iv. Avoid dronedarone. Contraindicated in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV HF
 - d. Calcium channel blockers (CCBs) (except for amlodipine and felodipine)
 - i. Negative inotropic activity
 - ii. Neurohormonal activation
 - iii. Amlodipine and felodipine have been proven safe in patients with HF and can be added when additional blood pressure reduction is needed.
 - e. Minoxidil
 - i. Fluid retention
 - ii. Stimulation of the renin-angiotensin-aldosterone system
 - f. Thiazolidinediones: Fluid retention
 - g. Metformin: Increased risk of lactic acidosis (black box warning)
 - h. Amphetamines (e.g., methylphenidate)
 - i. α - and β -agonist activity
 - ii. Tachycardia
 - iii. Atrial and ventricular arrhythmias
 - i. Nutritional supplements
 - j. Hormonal therapies
 - k. Cilostazol: Inhibition of phosphodiesterase type-3
 - l. Itraconazole: Negative inotropic activity
 - m. Pregabalin
 - i. Inhibition of calcium channels
 - ii. Lower extremity edema, HF exacerbation

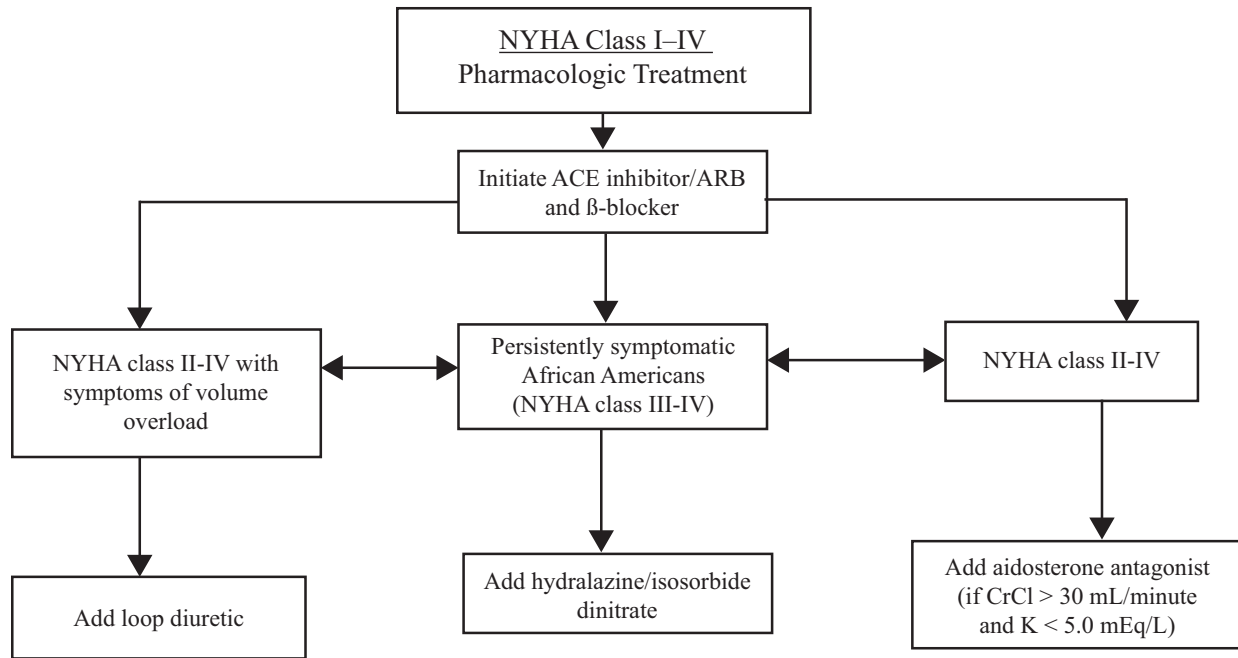


Figure 1. Algorithm for pharmacologic management of HF with EF.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CrCl = creatinine clearance; K = potassium; NYHA = New York Heart Association.

Adapted from Yancy CW, Jessup M, Bijkem B, et al. 2013 ACCF/AHA guidelines for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147-239.

In contrast to the large number of trials and the patients with systolic dysfunction who have been studied, there is a lack of objective data to guide therapy for patients with diastolic dysfunction. The following recommendations are based primarily on the consensus of CV experts.

C. HFpEF or Diastolic Dysfunction

1. General treatment goals of diastolic dysfunction
 - a. Control HTN according to published guidelines.
 - i. HTN impairs myocardial relaxation.
 - ii. HTN promotes cardiac hypertrophy.
 - b. Control tachycardia.
 - i. Tachycardia decreases the time for the ventricles and coronary arteries to fill with blood.
 - ii. Control of HR improves symptoms of HF.
 - iii. Can use β -blockers, or nondihydropyridine CCBs.
 - c. Reduce preload (cautiously).
 - i. Ventricular filling pressure is determined primarily by central blood volume.
 - ii. Patients with diastolic dysfunction are more preload-dependent for ventricular filling. Decreasing the preload too much may cause unexpected hypotension.
 - iii. Symptoms of breathlessness can be relieved using diuretics or nitrates.
 - d. Aggressively investigate, repair, and treat myocardial ischemia.
 - i. Myocardial ischemia impairs ventricular relaxation.
 - ii. Any ischemia possibly contributing to diastolic dysfunction warrants aggressive therapy.

2. Pharmacologic therapy for diastolic dysfunction
 - a. ACE inhibitors
 - i. Reduce hospitalizations.
 - ii. Treat HTN.
 - b. Angiotensin receptor blockers:
 - i. Reduce hospitalizations.
 - ii. Treat HTN.
 - c. Digoxin
 - i. No effect on all-cause mortality or on all-cause CV hospitalizations
 - ii. Possible increase in unstable angina admissions
 - d. β -Blockers, verapamil, and diltiazem: Benefits are targeted symptom relief.

Patient Case

4. P.M. is a 52-year-old man (weight 116 kg, height 178 cm) with a history of HTN and a transient ischemic attack 2 years ago. He visits his primary care doctor with the chief concern of several weeks of a “fluttering” feeling in his chest on occasion. He thinks the fluttering is nothing; however, his wife insists he have it checked. His current medications include metoprolol tartrate 50 mg twice daily and aspirin 81 mg/day. He is adherent to this regimen and has health insurance, but he does not like to make the trip to his primary care provider because it is a 3-hour drive. His laboratory data from his past visit were all within normal limits. His vital signs today include BP 130/78 mm Hg and HR 76 beats/minute. All laboratory values are within normal limits. An electrocardiogram (ECG) reveals an irregularly irregular rhythm, with no P waves, and a ventricular rate of 74 beats/minute. A diagnosis of AF is made. Which is the best approach for managing his AF?
 - A. Begin digoxin 0.25 mg/day.
 - B. Begin diltiazem CD 240 mg/day.
 - C. Begin warfarin 5 mg/day and titrate to a goal INR of 2.5.
 - D. Begin dabigatran 150 mg twice daily.

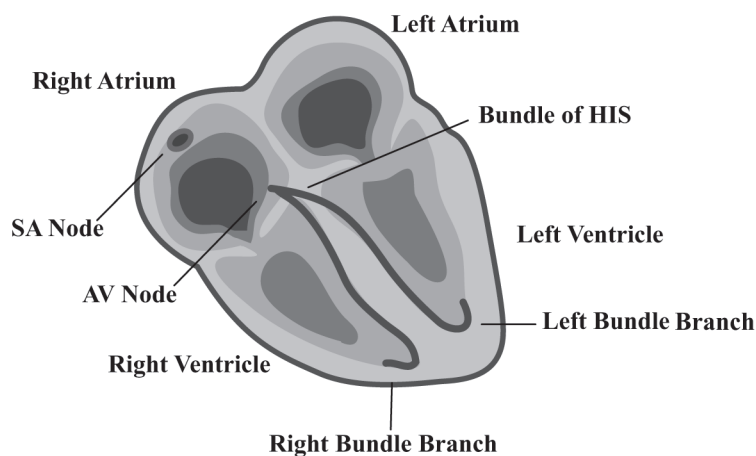
II. ATRIAL FIBRILLATION

- A. Background
 1. Prevalence
 - a. Most common arrhythmia: 2.2 million Americans
 - b. Prevalence increases with age
 - c. Common comorbidity in patients with valvular heart disease or HF
 2. Symptoms
 - a. Some patients have no symptoms.
 - b. At worst, an embolic event may occur or symptoms of HF may be present.
 - c. Potential symptoms that may be present to some degree include the following:
 - i. Palpitations
 - ii. Chest pain
 - iii. Dyspnea
 - iv. Fatigue
 - v. Light-headedness
 - d. Symptoms vary with ventricular rate, underlying LV functional status, AF duration, and individual patient perceptions.

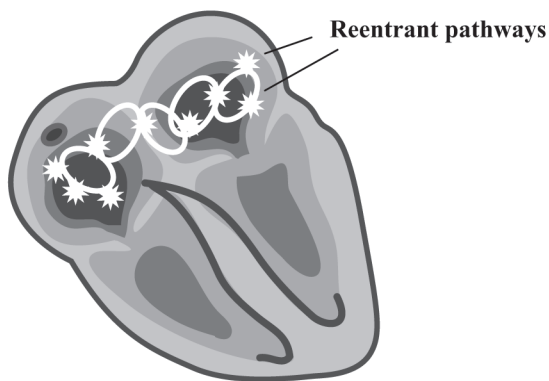
3. Classification (more than one of these may exist in a given patient):
 - a. Paroxysmal: Spontaneous self-termination within 7 days of onset
 - b. Persistent: Lasting more than 7 days
 - c. Long-standing persistent: Continuous duration of more than 12 months
 - d. Permanent: Present all the time, unable to return to normal sinus rhythm using pharmacologic or nonpharmacologic options
 - e. Nonvalvular: The absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

B. Pathophysiology

1. Cardiac conduction



- The impulse:
1. Is generated by the SA node.
 2. Propagates through atrial tissue.
 3. Reaches the AV node.
 4. Passes slowly through the AV node.
 5. Travels through the bundle of His.
 6. Is conducted simultaneously down the three bundle branches.
 7. Is distributed to the ventricular tissue by small embedded Purkinje fibers.



- The impulses:
1. Are generated in atrial tissues; \pm focal activation, with reentry pathways
 2. Bombard the AV node in a rapid and chaotic fashion.
 3. Are propagated by the AV node after it repolarizes from the last impulse.
 4. See 5–7 above.

Figure 2. Cardiac conduction and atrial fibrillation.

2. ECG findings
 - a. No P waves
 - b. Irregularly irregular rhythm
 - c. Rate may be fast or slow (depending on the rate of atrioventricular [AV] node conduction).

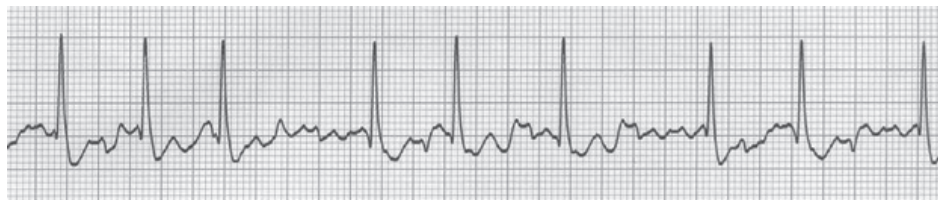


Figure 3. Electrocardiogram showing atrial fibrillation.

3. These abnormal impulses can have many causes (Table 7)

Table 7. Potential Causes of Atrial Fibrillation

Atrial Distension	High Adrenergic Tone
Chronic hypertension	Alcohol withdrawal
Mitral valve disease	Thyrotoxicosis
Cardiomyopathy	Sepsis
Congenital defects	Binge drinking
Pulmonary hypertension	Surgery
Acute pulmonary embolus	Sympathomimetics such as cocaine or amphetamines
Myocardial ischemia	Excessive theophylline, caffeine
Sleep apnea	
Emphysema or other lung diseases	

C. Pharmacologic Therapy

1. Ventricular rate control

- a. If patients have a rapid ventricular rate, AV node blockade is necessary.
- b. Goal HR (resting HR <80 beats/minute) is reasonable in symptomatic patients (class IIa recommendation). A more lenient rate control (resting HR <110 beats/minute) may be reasonable in patients who are asymptomatic and have LVEF preserved (class IIb recommendation).
- c. Goal is to reduce symptoms and possibly prevent tachycardia-induced cardiomyopathy.
- d. Select the best agent according to individual clinical response and concomitant disease states.
- e. These therapies have no effect on the cardioversion of AF:
 - i. β -Blockers
 - (a) Any agent with β -blockade can be used and dosed to the goal HR.
 - (b) Labetalol or carvedilol if additional α_1 -blockade is desirable (e.g., HTN)
 - (c) Effective for controlling exercise-associated HR increases
 - (d) Can be considered in patients with stable HF (only carvedilol, metoprolol CR/XL, or bisoprolol)
 - (e) Avoid in patients with Wolff-Parkinson-White syndrome.
 - ii. Nondihydropyridine CCBs: Verapamil or diltiazem
 - (a) Avoid use if there is concomitant systolic dysfunction.
 - (b) May be preferred over β -blocker in patients with asthma or severe chronic obstructive pulmonary disease
 - (c) Effective for controlling exercise-associated HR increases
 - (d) Avoid in patients with Wolff-Parkinson-White syndrome.

- iii. Digoxin
 - (a) Often ineffective alone for controlling ventricular rate in AF, especially during exercise or movement (because of minimal effectiveness with sympathetic stimulation)
 - (b) Can be included in regimen if patient has systolic HF
 - (c) May be effective if additional HR control is needed when a patient is receiving a β -blocker, diltiazem, or verapamil
 - (d) Avoid in patients with Wolff-Parkinson-White syndrome.
 - iv. Amiodarone
 - (a) May be used for rate control in patients with HF who do not have an accessory pathway
 - (b) May be used for rate control in patients who are refractory to other therapies such as β -blockers, nondihydropyridine CCBs, and digoxin
2. Rhythm control: Maintaining sinus rhythm (SR) offers no advantage over controlling the ventricular rate. However, in specific patients with intractable and intolerable symptoms (dyspnea and palpitations) despite adequate rate control or in patients for whom adequate ventricular rate control cannot be achieved, restoration and maintenance of SR may be desirable (Table 8).

Table 8. Summary of the Pros and Cons of Rate Control vs. Rhythm Control

	Pros	Cons
Rate control strategy	Easy to achieve and maintain; out-of-hospital therapy typical	Electrical and structural remodeling because of continued AF makes future attainment of SR virtually impossible, and safety not proven for younger patients
Rhythm control strategy	If patient is symptomatic with fatigue and exercise intolerance, these symptoms may improve if SR is attained (especially in the patient with HF); minimized structural atrial changes; acceptable for all age groups	Adverse effects of medications, cost of medications and monitoring, likelihood of AF recurrence; in-hospital stay may be necessary; high recurrence rate

AF = atrial fibrillation; HF = heart failure; SR = normal sinus rhythm.

3. Cardioversion in AF
- a. If cardioversion is attempted (electric or pharmacologic), the absence of atrial thrombi must be ensured.
 - i. Thrombi present plus cardioversion = 91% stroke rate.
 - ii. Without anticoagulation (caused by decreased or stagnant blood flow in the atria)
 - (a) AF for more than 48 hours = 15% rate of atrial thrombus.
 - (b) AF for more than 72 hours = 30% rate of atrial thrombus.
 - b. Ensure safe cardioversion by either:
 - i. Transesophageal echocardiogram to visualize the atria *or*
 - ii. Three or more weeks of therapeutic anticoagulation (INR greater than 2.0) (Table 9)

Table 9. Anticoagulation Strategies Surrounding Cardioversion of AF^a

Unstable	Synchronized Cardioversion, Anticoagulation Immediately Beforehand
Stable, duration <48 hours ^b	<p>ACCP (CHEST) guidelines</p> <ul style="list-style-type: none"> • Anticoagulate at presentation and continue through cardioversion <ul style="list-style-type: none"> – LMWH or UFH at full treatment doses • Anticoagulate for at least 4 weeks afterward, regardless of baseline risk of stroke <p>ACC/AHA/HRS AF guidelines</p> <ul style="list-style-type: none"> • During the first 48 hours, the need for anticoagulation before and after cardioversion may be based on the patient’s risk of thromboembolism
Stable, duration unknown or >48 hours	<p>ACCP (CHEST) guidelines</p> <ul style="list-style-type: none"> • Anticoagulate for 3 weeks before cardioversion <ul style="list-style-type: none"> – VKA with INR 2.0–3.0, LMWH at full treatment dose, or dabigatran <p>ACC/AHA/HRS AF guidelines</p> <ul style="list-style-type: none"> • Anticoagulate for 3 weeks before cardioversion regardless of the method (electrical or pharmacologic) used to restore sinus rhythm <ul style="list-style-type: none"> – Limited data support LMWH in this indication
TEE-guided cardioversion for stable, duration unknown or >48 hours	<p>ACCP (CHEST) guidelines</p> <ul style="list-style-type: none"> • TEE-guided therapy with abbreviated anticoagulation before cardioversion <ul style="list-style-type: none"> – LMWH or UFH at full treatment doses should be initiated at the time of TEE, and cardioversion should be performed within 24 hours of TEE if no thrombus is seen • Anticoagulate for 4 weeks after cardioversion regardless of baseline risk of stroke <p>ACC/AHA/HRS AF guidelines:</p> <ul style="list-style-type: none"> • If no identifiable thrombus seen on TEE, cardioversion is reasonable immediately after anticoagulation with UFH bridged to VKA or OAC (4 weeks)

^aPotential risk of conversion with amiodarone should be considered before treatment initiation.

^bNo randomized trials have compared different anticoagulation strategies in patients with AF <48 hours.

ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AF = atrial fibrillation; AHA = American Heart Association; HRS = Heart Rhythm Society; INR = international normalized ratio; IV = intravenous; LMWH = low-molecular-weight heparin; OAC = oral anticoagulant; TEE = transesophageal echocardiography; UFH = unfractionated heparin; VKA = vitamin K antagonist.

- c. Oral pharmacologic agents to induce or maintain sinus rhythm (choice of agent depends on the comorbidities)
 - i. Class Ic antiarrhythmics
 - (a) Flecainide and propafenone may be considered first-line therapies for patients without structural heart disease (see Figure 4).
 - (b) These agents may be used second or third line because of frequent dosing requirements and adverse effect profiles; some patients require hospitalization for initiation because of proarrhythmic effects; only about 50% efficacy at 1 year
 - (c) Contraindicated in patients with structural heart disease (including CHD, HF, left ventricular hypertrophy, and valvular heart disease)
 - ii. Class III antiarrhythmics
 - (a) Amiodarone: 85%–95% efficacy
 - (1) Has electrophysiologic properties of classes I–IV
 - (2) Oral loading dose required (400 mg two or three times/day × 2 weeks and then 400 mg/day for 4 weeks, followed by a 200-mg/day maintenance dose). Achieving a loading dose of 10 g is desirable. Many different regimens exist.
 - (3) Long half-life of about 60 days

- (4) In addition, has AV nodal blocking properties; may help control HR if AF recurs
- (5) Safe to use in patients with HF
- (6) Hepatically metabolized: cytochrome P450 (CYP) 3A4 substrate; inhibitor of CYP3A4, CYP1A2, CYP2C9, and CYP2D6, and P-glycoprotein
- (7) Minimal incidence of ventricular arrhythmias
- (8) Drug interactions (many)
 - (A) Digoxin: Increased digoxin exposure. Lower initial digoxin dose by 50%.
 - (B) Warfarin: Increased warfarin exposure. Lower warfarin dose by 25%–30%.
 - (C) Simvastatin: Increased simvastatin exposure. Do not exceed dose of 20 mg/day.
 - (D) Lovastatin: Increased lovastatin exposure. Do not exceed dose of 40 mg/day.
 - (E) β -Blockers: Additive bradycardia
 - (F) Nondihydropyridine CCBs: Additive bradycardia
- (9) Extensive monitoring for noncardiac adverse effects
 - (A) Liver function tests (LFTs): Baseline and every 6 months
 - (B) Thyroid function tests: Baseline and every 6 months
 - (C) Chest radiography: Baseline and annually
 - (D) Pulmonary function tests (including DLCO(2) [carbon dioxide diffusion in the lungs]): Baseline and for unexplained dyspnea or chest radiographic abnormalities. Discontinue if pulmonary fibrosis occurs.
 - (E) Ophthalmologic examination: For symptoms of visual impairment. Discontinue if optic neuritis occurs.
 - (F) Skin toxicities: “Blue skin” syndrome and sunburn
 - (G) Neurologic toxicity: Monitor for neuropathy.
 - (H) Gastrointestinal adverse effects
- (b) Sotalol: 50%–60% efficacy
 - (1) Renal excretion; hence, dose adjustment and vigilant corrected QT (QTc) interval monitoring necessary in renal impairment. Recommended starting dose is 80 mg twice daily.
 - (2) Should be initiated in the hospital for a minimum of 3 days, where QTc, serum electrolytes (e.g., K and Mg), and renal function can be monitored
 - (3) Contraindicated in patients with HF, CrCl less than 40 mL/minute, or QTc interval greater than 440 milliseconds, sinus bradycardia, second- or third-degree AV block without functioning pacemaker
- (c) Dofetilide: 50%–60% efficacy
 - (1) Must be initiated in the hospital (3-day stay) so QTc, serum electrolytes (K, Mg), can be monitored
 - (2) Dose adjusted according to renal function and QTc interval response. Renal dosing: If CrCl is greater than 60 mL/minute, 500 mcg twice daily; CrCl 40–60 mL/minute, 250 mcg twice daily; CrCl 20–39 mL/minute, 125 mcg twice daily; CrCl less than 20 mL/minute, contraindicated
 - (3) Hepatically metabolized by CYP3A
 - (4) Renal elimination through renal cationic secretion; check QTc interval if renal function acutely declines
 - (5) Contraindicated in patients with CrCl less than 20 mL/minute or QTc interval greater than 400 milliseconds (or 500 milliseconds for patients with ventricular conduction abnormalities)
 - (6) Safe to use in patients with HF
 - (7) Drug interactions

- (A) Cimetidine, verapamil, itraconazole, ketoconazole, hydrochlorothiazide, prochlorperazine, megestrol, dolutegravir, and trimethoprim alone or in combination with sulfamethoxazole: Avoid
 - (B) CYP3A4 inhibitors: Increased dofetilide exposure, so use with caution
 - (C) Triamterene, metformin, amiloride: Increased dofetilide exposure, use with caution
- (d) Dronedarone: 21%–25% efficacy
- (1) Amiodarone analog lacking the iodine moiety that contributes to the pulmonary, thyroid, hepatic, and ocular toxicity of amiodarone
 - (2) Has electrophysiologic properties of classes I–IV with minimal proarrhythmic effects
 - (3) Dose: 400 mg twice daily with morning and evening meal
 - (4) Hepatically metabolized; CYP3A4 substrate and moderate CYP3A4, CYP2D6, and P-glycoprotein inhibitors
 - (5) Half-life is 13–19 hours.
 - (6) Marked increases in SCr (prerenal azotemia and acute renal failure) have been reported. Small increase in creatinine by 0.1 mg/dL, probably as a result of inhibition of creatinine’s tubular secretion. Rapid onset, will plateau after 7 days and is reversible
 - (7) Contraindicated in permanent AF, NYHA class II or III HF with recent decompensation necessitating hospitalization, NYHA class IV HF, severe liver impairment, HR less than 50 beats/minute, concurrent use of strong CYP3A4 inhibitors or QTc interval–prolonging agents, history of amiodarone-induced hepatotoxicity or pulmonary toxicity, pregnancy, or QTc interval greater than 500 milliseconds
 - (8) One meta-analysis found dronedarone less effective than amiodarone for the maintenance of sinus rhythm but with fewer adverse effects.
 - (9) Drug interactions
 - (A) Digoxin: Increased digoxin exposure; lower digoxin dose by 50%.
 - (B) Diltiazem, verapamil, β -blockers: Excessive bradycardia; initiate these drugs at lowest dose. Diltiazem and verapamil can increase dronedarone exposure, so monitor ECG.
 - (C) Statins: Increased statin exposure. Limit dose of simvastatin to 10 mg/day and lovastatin to 20 mg/day.
 - (D) Dabigatran: In patients with moderate renal impairment (CrCl 30–50 mL/minute), dronedarone increases dabigatran exposure, dabigatran dose reduction to 75 mg twice daily is recommended.
 - (E) Strong CYP3A4 inhibitors and inducers: *Avoid*.
 - (F) Cyclosporine, tacrolimus, sirolimus: Increased exposure of these agents; monitor serum concentrations closely
 - (10) Other safety issues
 - (A) Liver injury: According to postmarketing surveillance, dronedarone has been associated with rare but severe hepatic liver injury.
 - (B) Pulmonary toxicity: In postmarketing surveillance, cases of interstitial lung disease, including pneumonitis and pulmonary fibrosis, have been reported. Patients should report any new signs of dyspnea or nonproductive cough.

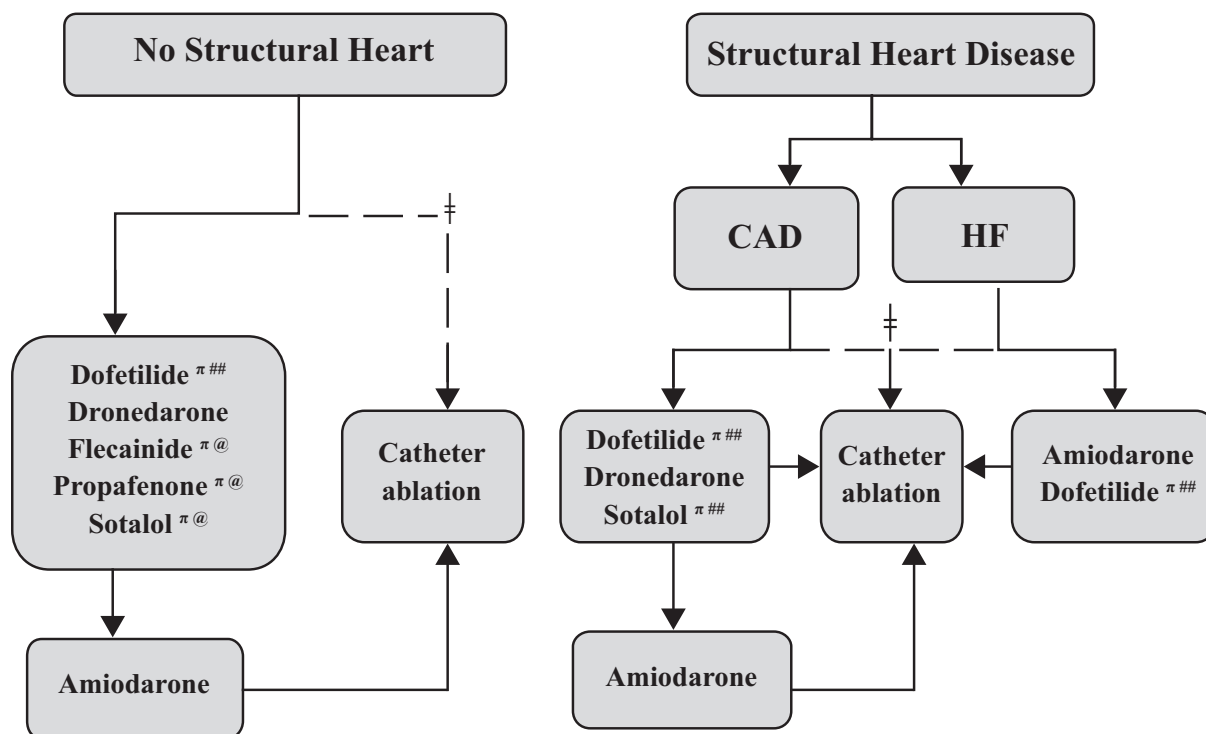


Figure 4. Options for rhythm control in patients with paroxysmal and persistent atrial fibrillation.

CAD = coronary artery disease; HF = heart failure.

Catheter ablation is the only recommended first-line therapy for patients with paroxysmal AF (class IIa recommendation).

π Not recommended with severe left ventricular hypertrophy (LVH) (wall thickness >1.5 cm).

Use with caution in patients at risk for torsades de pointes ventricular tachycardia.

@ Should be combined with AV nodal blocking agents.

Adapted with permission from January CT, Wann SL, Sacco RL, et al.; AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation. Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and Heart Rhythm Society. Circulation 2014;130:2071.

4. Antithrombotic therapy

- a. The average annual stroke rate is 5% per year without anticoagulation.
 - i. A patient's individual risk may vary from about 1% to 20% per year depending on his or her risk factors.
 - ii. This risk is independent of current cardiac status (i.e., sinus rhythm or AF).
- b. Risk stratification and treatment determination (Tables 10 and 11)

Table 10. Risk Stratification for Antithrombotic Therapy Using the CHA₂DS₂VASc Score^a

Risk Factor	Score
CHF or LVEF ≤40%	1
Hypertension	1
Age ≥75	2
Diabetes	1
Stroke, TIA, thromboembolism	2
Vascular disease	1
Age 65–74	1
Sex category (female)	1

^aFor use in patients with nonvalvular atrial fibrillation. Maximum point value is 9.

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

Table 11. Thromboembolic Event Risk Based on CHA₂DS₂VASc Score

CHA ₂ DS ₂ VASc Score	Patients (n = 7329)	Adjusted Stroke Rate (%/year)
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

Table 12. Recommendations for Antithrombotic Therapy Based on CHA₂DS₂VASc Score

CHA ₂ DS ₂ VASc Score = 0	CHA ₂ DS ₂ VASc Score = 1	CHA ₂ DS ₂ VASc Score ≥ 2
Reasonable to omit antithrombotic therapy and aspirin	No antithrombotic therapy, OAC, or aspirin	OAC

OAC = oral anticoagulant.

Table 13. Comparison of New Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Factor II	Factor Xa	Factor Xa	Factor Xa
Impact on coagulation assay	aPTT (2–3 ×) ↑ INR 40% ↑	aPTT 40% ↑ INR 40% ↑	↑ aPTT and INR	↑ aPTT, PT, and INR
Peak	1–3 hours	2–4 hours	1–3 hours	1–2 hours
Half-life	14–17 hours	9–13 hours	8–15 hours	10–14 hours
Percentage undergoing renal elimination	80%	33%	25%	~ 50%
Dialyzable	Yes	No	No	No
CYP metabolism	No	30% CYP3A4	15% CYP3A4	No
P-glycoprotein substrate	Yes	Yes	Yes	Yes

aPTT = activated partial thromboplastin time; CYP = cytochrome P450; INR = international normalized ratio.

- c. Dabigatran
 - i. Direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF
 - ii. Dose: CrCl greater than 30 mL/minute, 150 mg twice daily; CrCl 15–30 mL/minute, 75 mg twice daily; CrCl less than 15 mL/minute, no dosing recommendations available; swallow capsules whole (do not break, crush, or chew)
 - iii. Place in therapy: Patients with AF and at least one additional risk factor for stroke. Should consider individual clinical features, including the ability to adhere to twice-daily dosing, patient preferences, and cost
 - iv. Stability: Once a bottle is opened, the medication should be used within 4 months to maintain appropriate potency.
 - v. Converting from or to warfarin or parenteral anticoagulants (Table 14)

Table 14. Dabigatran Conversion Strategies to and from Oral and Parenteral Anticoagulants

Converting from or to Warfarin	
CrCl ≥50 mL/minute	Start warfarin 3 days before discontinuing dabigatran
CrCl 31–50 mL/minute	Start warfarin 2 days before discontinuing dabigatran
CrCl 15–30 mL/minute	Start warfarin 1 day before discontinuing dabigatran
CrCl <15 mL/minute	No dosing recommendations are available
Converting from or to Parenteral Anticoagulants	
Start dabigatran 0–2 hours before the next dose of the parenteral drug was to have been administered (e.g., low molecular weight heparin) or when a continuously administered parenteral drug is discontinued (e.g., intravenous unfractionated heparin)	
For patients currently taking dabigatran, wait 12 hours (CrCl >30 mL/minute) or 24 hours (CrCl <30 mL/minute) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant	
Converting from Warfarin to Dabigatran	
Discontinue warfarin and start dabigatran when the INR is below 2.0	

Note: Because dabigatran can contribute to an increased INR, the INR will better reflect warfarin’s effect after dabigatran has been discontinued for at least 2 days.

CrCl = creatinine clearance; INR = international normalized ratio.

- vi. Drug interactions: Dabigatran is a substrate of P-glycoprotein.
 - (a) P-glycoprotein inducers (e.g., only rifampin mentioned in package labeling) should be avoided; however, inhibitors such as ketoconazole, verapamil, dronedarone, amiodarone, quinidine, and clarithromycin do not require dose adjustments in patients with normal renal function. However, when using dabigatran in combination with dronedarone and ketoconazole (P-glycoprotein inhibitors) in patients with moderate renal dysfunction (CrCl 30–50 mL/minute), consider reducing the dabigatran dose to 75 mg twice daily.
 - (b) Dabigatran should not be used in combination with P-glycoprotein inhibitors in the setting of severe renal impairment (CrCl less than 30 mL/minute).
 - vii. Bleeding: In patients with AF at risk of stroke, both doses of dabigatran compared with warfarin (INR 2–3) have lower risks of both intracranial and extracranial bleeding in patients younger than 75 years. In those 75 years and older, intracranial bleeding risk is lower, but extracranial bleeding risk is similar to or higher than with both doses of dabigatran compared with warfarin. However, incidence of gastrointestinal (GI) bleeding is higher compared with warfarin.
- d. Rivaroxaban
- i. Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF
 - ii. Dose: CrCl greater than 50 mL/minute, 20 mg/day with evening meal; CrCl 15–50 mL/minute, 15 mg/day with evening meal; CrCl less than 15 mL/minute, avoid use; may be administered via nasogastric tube or gastric feeding tube (crush tablets and suspend in 50 mL of water). Tablets may also be crushed and mixed in applesauce.
 - iii. Place in therapy: Should consider individual clinical features, including the ability to adhere to regimen, patient preferences, and cost
 - iv. Converting warfarin to rivaroxaban: Discontinue warfarin and initiate rivaroxaban once INR is below 3.0.
 - v. Converting from parenteral anticoagulants other than warfarin to rivaroxaban: Administer rivaroxaban 0–2 hours before the next scheduled evening dose of current anticoagulant (e.g., low molecular weight heparin) or at the same time as when a continuously administered parenteral drug is discontinued (e.g., intravenous unfractionated heparin).
 - vii. Drug interactions. Rivaroxaban is a substrate of cytochrome P450 (CYP) 3A4/5 and P-glycoprotein.
 - (a) Combined strong CYP3A4 and P-glycoprotein inhibitors (ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, conivaptan): Avoid administration of rivaroxaban.
 - (b) Combined strong CYP3A4 and P-glycoprotein inducers (carbamazepine, phenytoin, rifampin, St. John's wort): Avoid administration of rivaroxaban.
 - (c) Combined P-glycoprotein inhibitors and weak or moderate CYP3A4 inhibitors (ranolazine, erythromycin, azithromycin, quinidine, amiodarone, felodipine, diltiazem, verapamil, dronedarone) in the setting of renal impairment (CrCl 15–80 mL/minute) Avoid administration of rivaroxaban.
 - viii. Bleeding: No difference in the rates of major and nonmajor bleeding between rivaroxaban and warfarin; however, a significant reduction was seen in intracranial and fatal bleeding in the rivaroxaban group. However, incidence of GI bleeding is higher compared with warfarin.
- e. Apixaban
- i. Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF

- ii. Dose: 5 mg twice daily. In patients with at least two of the following characteristics (age 80 years or older, body weight ≤ 60 kg, or SCr of ≥ 1.5 mg/dL) the recommended dose is 2.5 mg twice daily; CrCl less than 15 mL/minute, no specific recommendations. End-stage renal disease (ESRD) maintained on hemodialysis, 5 mg twice daily. In patients with ESRD maintained on hemodialysis who are ≥ 80 years of age or ≤ 60 kg, 2.5 mg twice daily. May be administered via nasogastric tube (crush tablets and suspend in 60 mL D5W and administer immediately).
 - iii. Place in therapy: Should consider individual clinical features, including the ability to adhere to regimen, patient preferences, and cost
 - iv. Converting from warfarin: Discontinue warfarin and start apixaban once the INR is below 2.0.
 - v. Converting to parenteral anticoagulants other than warfarin: Discontinue current anticoagulant; initiate apixaban at the time of the next scheduled dose.
 - vi. Drug interactions: Apixaban is a substrate of CYP3A4 and P-glycoprotein.
 - (a) Combined strong dual CYP3A4 and P-glycoprotein inhibitors (ketoconazole, itraconazole, ritonavir, or clarithromycin): Decrease dose of apixaban to 2.5 mg twice daily. If already taking reduced dose of apixaban, avoid use.
 - (b) Combined strong dual inducers of CYP3A4 and P-glycoprotein (rifampin, carbamazepine, phenytoin, phenobarbital, or St. John's wort): Avoid concomitant use.
- f. Edoxaban
- i. Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF
 - ii. Dose: 60 mg once daily in patients with CrCl > 50 mL/min to ≤ 95 mL/min. Reduce dose to 30 mg once daily if CrCL is between 15 mL/min and 50 mL/min. There are no data on administering edoxaban via feeding tubes or with crushing the medication to mix with other foods or liquids.
 - iii. Place in therapy: Should consider individual clinical features, including the ability to adhere to regimen, patient preferences, and cost
 - iv. Converting from warfarin: Discontinue warfarin and initiate edoxaban with the INR is ≤ 2.5
 - v. Converting from oral anticoagulants other than warfarin: discontinue current oral anticoagulant and initiate edoxaban at the time the next scheduled dose of oral anticoagulant is due
 - vi. Converting from LMWH: discontinue LMWH and initiate edoxaban at time of next scheduled dose of LMWH
 - vii. Converting from UFH: discontinue the UFH infusion and initiate edoxaban 4 hours later
 - viii. Converting to warfarin: If receiving 60 mg dose, reduce dose to 30 mg and initiate warfarin. If receiving 30 mg dose, reduce dose to 15 mg and initiate warfarin. Once INR is ≥ 2 , discontinue edoxaban
 - ix. Converting to non-vitamin K dependent oral anticoagulants: Discontinue edoxaban and initiate other oral agent at the time the next dose of edoxaban is due
 - x. Converting to parenteral anticoagulants: discontinue edoxaban and initiate parenteral anticoagulant at the time the next dose of edoxaban is due
 - xi. Drug Interactions: Edoxaban undergoes minimal metabolism via hydrolysis, conjugation and oxidation by CPY3A4
 - (a) Anticoagulants – avoid combination
 - (b) Rifampin – avoid combination
- g. Warfarin
- i. Inhibits vitamin K-dependent clotting factors II, VII, XI, X. Also inhibits anticoagulant proteins C and S. Racemic mixture of R and S-isomers:
 - (a) S-isomer more potent vitamin K antagonist

- (b) S-isomer metabolized primarily by CYP2C9
- (c) R-isomer metabolized primarily by CYP3A4
- ii. Dosing is based on what is needed to achieve an INR goal of 2–3 for patients with nonvalvular atrial fibrillation. For patients with mitral stenosis, prosthetic heart valves, prior thromboembolism, or persistent atrial thrombus on TEE, an INR goal of 2.5–3.5 or even higher may be indicated.
- iii. Initial starting dose is usually 5 mg/day. Lower starting dose (2–3 mg/day) should be considered in patients with the following: advanced age, low body weight, drug interactions, malnourishment, heart failure, hyperthyroid state, low albumin, or liver disease.
 - (a) Half-lives of vitamin K–dependent clotting factor VII, 6 hours; factor IX, 24 hours; factor X, 36 hours; factor II, 72 hours
 - (b) Adjusting dose: Watch for trends; remember that the INR seen today is the result of the doses given in the past 4–5 days. Takes 5–7 days to reach full effect, given the half-life of factor II
 - (c) If INR is out of therapeutic range, increase or decrease cumulative weekly warfarin dose by 5%–20% depending on INR; if INR is high (generally above 4.5), may hold one or two doses and resume at a lower dose
 - (d) If INR previously stable or therapeutic and single out-of-range INR is 0.5 or less above or below therapeutic range, current dose can be continued, and recheck INR within 1–2 weeks.
 - (e) In general, no need to adjust if INR is within 0.1 of goal (but monitor more closely)
- iv. Place in therapy: Consider individual clinical features. May be optimal for patients with severe renal impairment, mechanical heart valves, valvular atrial fibrillation, and those that are stable on warfarin
- v. Drug interactions
 - (a) Reduced warfarin absorption (e.g., cholestyramine, sucralfate)
 - (b) Enzyme induction (decreases INR and warfarin effects)
 - (1) CYP3A4 inducers (e.g., rifampin, carbamazepine, phenobarbital, St. John’s wort)
 - (2) Other (e.g., griseofulvin, nafcillin, dicloxacillin, phenytoin [inhibition, then induction])
 - (3) Delay in onset and offset
 - (c) Enzyme inhibition (increases INR and warfarin effects)
 - (1) S-warfarin (CYP2C9 inhibitors) (e.g., metronidazole, trimethoprim/sulfamethoxazole, fluconazole, isoniazid, fluoxetine, sertraline, amiodarone, clopidogrel, lovastatin)
 - (2) R-warfarin (CYP3A3/4/5 inhibitors) (e.g., omeprazole, clarithromycin, erythromycin, “azole” antifungals, nefazodone, fluoxetine, amiodarone, cyclosporine, sertraline, grapefruit juice, ciprofloxacin, norfloxacin, protease inhibitors, diltiazem, verapamil, isoniazid, metronidazole)
 - (d) Drugs with antiplatelet effects (e.g., ginkgo, garlic, aspirin, NSAIDs, selective serotonin reuptake inhibitors); NSAIDs and aspirin also increase the risk of ulcers, providing a site from which to bleed.
 - (e) Drugs that reduce warfarin clearance (e.g., propafenone)
 - (f) Drugs that increase the degradation of clotting factors (e.g., levothyroxine)
- vi. Bleeding: Incidence 2.4%–29%, life threatening 2%–8%. Epistaxis, hematuria, GI hemorrhage, bleeding gums. Easy bruising often occurs with therapeutic INR.
 - (a) Minor hemorrhage increased with therapeutic warfarin therapy
 - (b) Major hemorrhage not increased with warfarin therapy at INR 2–3
 - (c) Risk of intracranial hemorrhage increased with INR greater than 4

Patient Case

5. H.D. is a 67-year-old man with a history of HTN, moderate mitral valve insufficiency, and AF for 4 years. His medications include ramipril 5 mg twice daily, sotalol 120 mg twice daily, digoxin 0.125 mg/day, and warfarin 5 mg/day. He visits his primary care physician today after being discharged from the emergency department with increased fatigue on exertion, palpitations, and lower extremity edema. His vital signs today include BP 115/70 mm Hg and HR 88 beats/minute, and all laboratory results are within normal limits; however, his lower extremity edema has worsened. His INR is 2.8. His ECG shows AF. An echocardiogram shows an LVEF of 35%–40%. H.D.'s physician would like to initiate a rhythm control approach. Which is the best approach for managing his AF?
- A. Discontinue sotalol and begin metoprolol succinate 12.5 mg/day.
 - B. Discontinue sotalol and begin dronedarone 400 mg twice daily.
 - C. Discontinue sotalol and begin amiodarone 400 mg twice daily, tapering to goal dose of 200 mg/day for the next 6 weeks.
 - D. Continue sotalol and add metoprolol tartrate 25 mg twice daily.

D. Nonpharmacologic Therapies

1. Electrical cardioversion (low-energy cardioversion; sedation highly desirable; can be used in an emergency if patient is hemodynamically unstable)
2. AV nodal ablation: Ablate AV node and chronically pace the ventricles.
3. Pulmonary vein ablation: Ablates the origin of the abnormal atrial foci, which is often near the pulmonary vein–atrial tissue intersection

III. HYPERTENSION

Definition: Hypertension is considered a BP of 140/90 mm Hg or higher.

A. Background

1. Statistics
 - a. Most common chronic disease in the United States
 - b. Affects about 78 million Americans
 - c. Major modifiable risk factor for CV disease and stroke
 - d. HTN is adequately controlled in only 52.5% of patients with HTN.
2. Etiology
 - a. Essential HTN: 90% (no identifiable cause)
 - i. Contributed to by obesity
 - ii. Evaluate Na intake
 - b. Secondary HTN
 - i. Primary aldosteronism
 - ii. Renal parenchymal disease
 - iii. Thyroid or parathyroid disease
 - iv. Medications (e.g., cyclosporine, NSAIDs, sympathomimetics)
 - v. Pheochromocytoma
3. Diagnosis
 - a. Periodic screening for all people older than 21 years
 - b. Patient should be seated quietly in chair for at least 5 minutes.
 - c. Use appropriate cuff size (bladder length at least 80% the circumference of the arm).

- d. Take BP at least twice, separated by at least 2 minutes.
- e. The average BP on two separate visits is required to diagnose HTN accurately.
- 4. Benefits of lowering BP
 - a. Decreased risk of stroke (by 40%)
 - b. Decreased risk of MI (by 25%)
 - c. Decreased risk of HF (by 50%)
- 5. Effects of lifestyle modifications on BP (Table 15)

Table 15. Recommended Lifestyle Modifications

Modification	Recommendation	Approximate Systolic BP Reduction
Weight reduction	Maintain a normal body weight (BMI 18.5–24.9 kg/m ²)	5–20 mm Hg per 10-kg weight loss
Adopt DASH eating plan (includes substantial potassium intake)	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Reduce sodium intake	Reduce sodium intake to ≤2400 mg/day Reducing sodium intake further to ≤1500 mg/day is associated with greater BP reduction Reducing sodium intake by at least 1000 mg/day will lower BP if desired daily sodium intake goal is not achieved	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes/day most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to: Men: 2 drinks/day (24 ounces of beer, 10 ounces of wine, or 3 ounces of 80 proof whiskey) Women and those of lower body weight: 1 drink/day	2–4 mm Hg

BMI = body mass index; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension.

B. Therapeutic Management

- 1. Patient classification and management in adults: Primary classification based on systolic BP (Table 16)

Table 16. Classification of BP and Hypertension and Lifestyle Modification Recommendations

BP Classification	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Lifestyle Modification or Pharmacologic Therapy	
BP goal ^a	< 140	<i>and</i>	< 90	Encourage
Stage 1 hypertension	140–159	<i>or</i>	90–99	Yes/consider
Stage 2 hypertension	> 160	<i>or</i>	> 100	Yes/2 medications

^aThis is the blood pressure (BP) goal for most patients. Lower targets maybe needed in certain patient populations. See Table 17. Weber MA, Schiffrin EL, White WB. Clinical practice guidelines for the management of hypertension in the community. A statement by the American Society of Hypertension and the International Society of Hypertension. Am J Hypertens. doi:10.1111/jch.12237.

Patient Cases

6. D.W. is a 50-year-old African American man being discharged from the hospital after an acute MI. His medical history is significant for HTN. He was taking hydrochlorothiazide 25 mg/day before hospitalization. An echocardiogram before discharge showed an LVEF of more than 60%. His vital signs include BP 150/94 mm Hg and HR 80 beats/minute. Which is the best approach for managing his HTN?
- A. Discontinue hydrochlorothiazide and add diltiazem.
 - B. Continue hydrochlorothiazide and add metoprolol.
 - C. Discontinue hydrochlorothiazide and add losartan.
 - D. Continue hydrochlorothiazide and add losartan.
7. T.J. is a 45-year-old white woman with a history of type 2 diabetes mellitus treated with glyburide 5 mg/day. She presents to the clinic for a routine follow-up of her diabetes. Her vital signs today include BP (average of two readings) 138/88 mm Hg and HR 70 beats/minute. Her laboratory results are as follows: Na 140 mEq/L, K 4.0 mEq/L, chloride 102 mEq/L, bicarbonate 28 mEq/L, BUN 14 mg/dL, SCr 1.0 mg/dL, 24-hour urine albumin 36 mg/g creatinine. Of note, at her last visit her BP was 136/85 mm Hg. Which is the best approach for managing her HTN at this time?
- A. Begin lifestyle modifications only.
 - B. Begin lifestyle modifications and add amlodipine 5 mg/day.
 - C. Begin lifestyle modifications and add lisinopril 2.5 mg/day.
 - D. Begin lifestyle modifications and add atenolol 25 mg/day.

2. Select treatment goal.
- a. The optimal BP goal will vary depending on age, concomitant disease states, and guideline reference. Lower targets may be necessary in different patient populations such as those with chronic kidney disease (CKD) or diabetes mellitus; blacks; and the elderly.
 - b. Several guidelines address BP goals for specific disease states. These goals are outlined in Tables 17.

Table 17. Goal BP Values Recommended by Various Organizations

Patient Population	Goal BP (mm Hg)
General population age ≥ 60 years ^a	<150/90
General population age <60 years ^a	<140/90
For adults age 18–80 years ^b	<140/90
Patients with diabetes mellitus ≥ 18 years ^c (a lower systolic target of < 130 mmHg may be appropriate in younger patients if can be achieved without undue treatment burden).	<140/80
Pregnancy with diabetes	110–129/65–79
Patients with CKD ^{a,d}	$\leq 140/90$
^a For those ≥ 18 years	
In adults both with and without diabetes having a urine albumin excretion <30 mg/24 hours (or equivalent) whose BP is consistently >140/90 mm Hg ^d	
In adults both with and without diabetes having a urine albumin excretion of ≥ 30 mg/24 hours (or equivalent) whose BP is consistently >130/80 mm Hg systolic ^c	$\leq 130/80$
Patients with HFpEF or HFrEF^e	<130/80
Elderly patients ^f Age 55–79	SBP ≤ 140
Age ≥ 80	SBP 140–145
Exceptions:	
(1) In patients for whom an SBP <150 mm Hg is readily and safely obtained with just one or two drugs, further intensification of treatment to achieve a value <140 mm Hg may be considered	
(2) In patients whose SBP remains ≥ 150 mm Hg, the lowest safely achieved SBP ≥ 150 mm Hg is acceptable when (a) goal has not been achieved, despite taking well-selected medications that are appropriately dosed; (b) unacceptable adverse effects occur, particularly postural hypotension that may result in disastrous consequences secondary to physical injury; and (c) attempts to reach target SBP have resulted in the DBP being reduced to a potentially dangerous level (<65 mm Hg)	

^aJames PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC8). JAMA 2014;507-20.

^bWeber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. A statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens 2014;14-26.

^cStandards of medical care in diabetes -2014. Diabetes Care. 2014;37(Suppl 1): S14-S80.

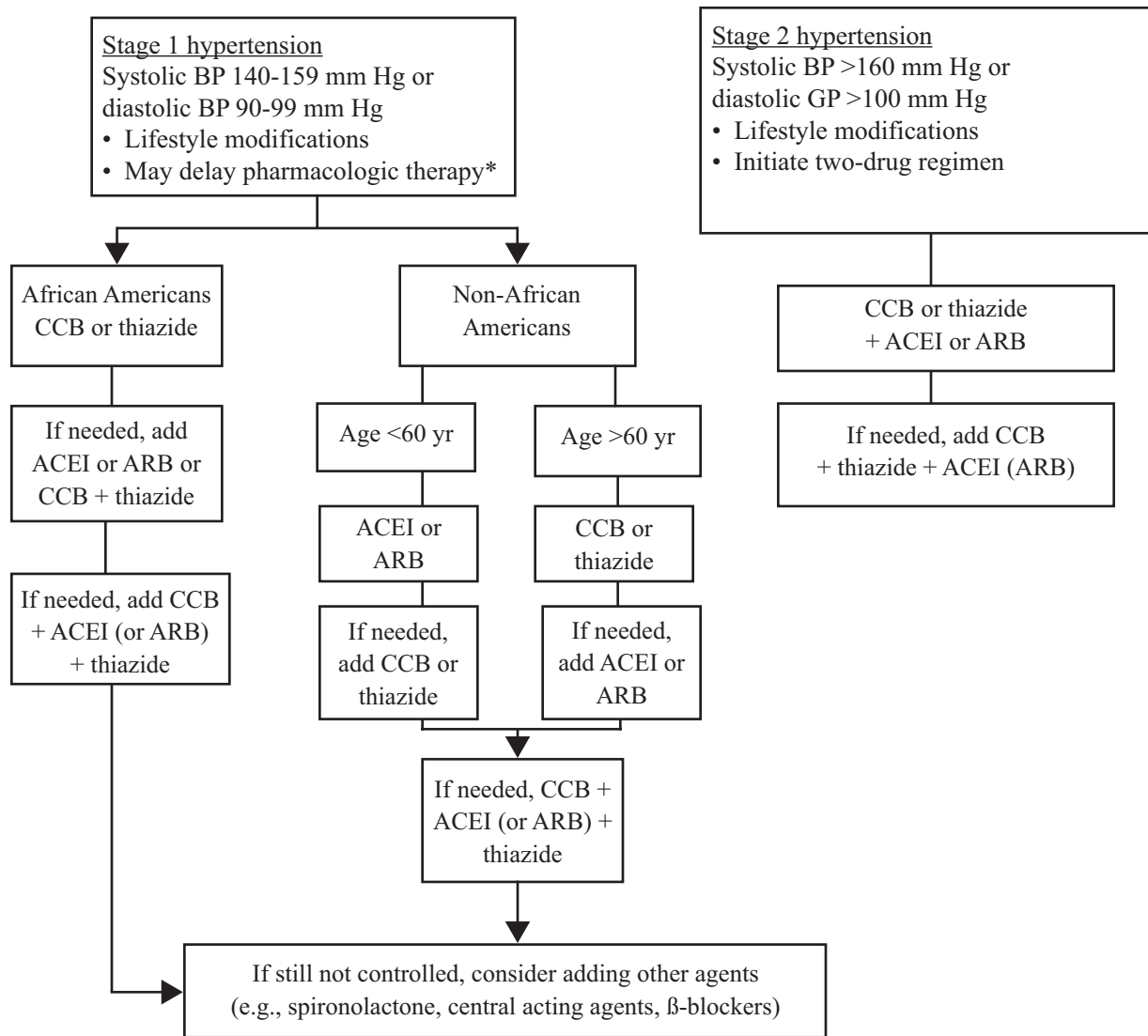
^dKDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl 2012;2:341-2.

^eYancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-327.

^fAronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2011;57:2037-114.

BP = blood pressure; CKD = chronic kidney disease; DBP = diastolic blood pressure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; SBP = systolic blood pressure.

3. HTN treatment algorithm



*Time interval to recheck BP should be based on patient’s risk and adverse outcomes.

Figure 5. Treatment algorithm for hypertension.

James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC8). JAMA 2013. Available at <http://jama.jamanetwork.com/article.aspx?articleid=1791497>.

Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. A statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens 2013. Available at www.ash-us.org/documents/ASH_ISH-Guidelines_2013.pdf.

ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CDC = Centers for Disease Control and Prevention.

4. Select appropriate therapy.

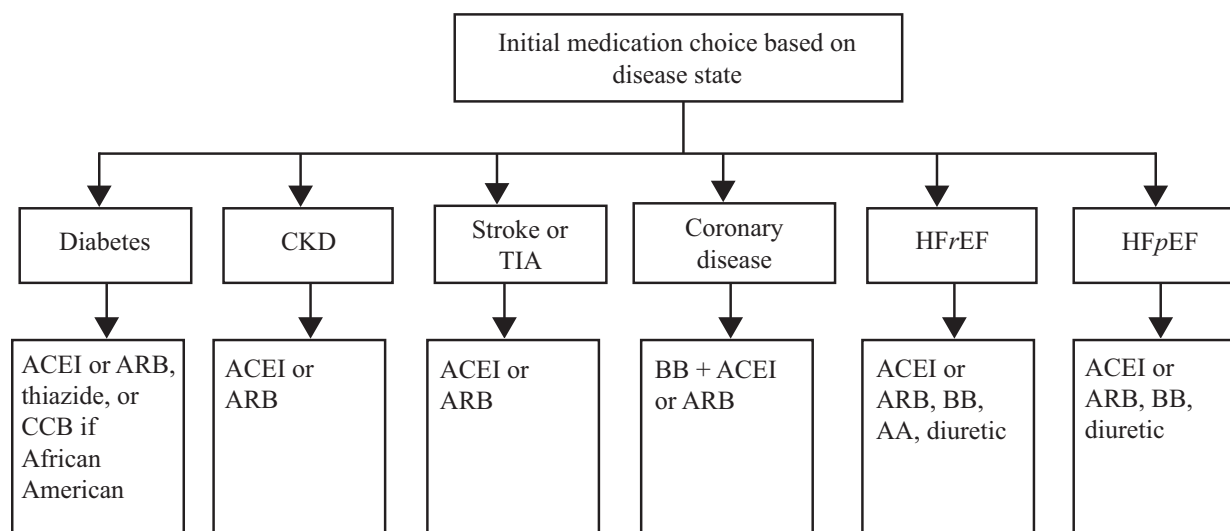


Figure 6. Selecting appropriate therapy for hypertension based on disease state.

James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC8). *JAMA* 2014;311:507-20.

Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. A statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens* 2014;16:14-26.

AA = aldosterone antagonist; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = β -blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; TIA = transient ischemic attack.

5. Considerations with specific antihypertensive agents

- a. β -Blockers
 - i. Caution with asthma or severe chronic obstructive pulmonary disease (especially higher doses) because of pulmonary β -receptor blockade
 - ii. Greater risk of developing diabetes compared with an ACE inhibitor, ARB, and CCB; use caution in patients at high risk of diabetes mellitus (e.g., family history, obese)
 - iii. May mask some signs of hypoglycemia in patients with diabetes mellitus
 - iv. May cause depression
- b. Thiazides
 - i. May worsen gout by increasing serum uric acid
 - ii. Greater risk of developing diabetes compared with ACE inhibitor, ARB, and CCB; use caution in patients at high risk of diabetes mellitus (e.g., family history, obese)
 - iii. May assist in the management of osteoporosis by preventing urine calcium loss
- c. ACE inhibitors and ARBs
 - i. Contraindicated in pregnancy
 - ii. Contraindicated with bilateral renal artery stenosis
 - iii. Monitor K closely, especially if renal insufficiency exists or another K-sparing drug is used.
 - iv. Presence of diabetic nephropathy should influence the choice of ACE inhibitor versus ARB.
- d. Direct renin antagonist
 - i. Aliskiren
 - ii. Contraindicated in pregnancy
 - iii. Contraindicated in patients with diabetes when used in combination with ACE inhibitors or ARBs because of increased risk of renal impairment, hyperkalemia, and hypotension

- iv. Avoid use in combination with cyclosporine or itraconazole
 - v. Avoid concurrent use with ACE inhibitors or ARBs in patients with renal impairment (CrCl <60 mL/minute)
6. Considerations within specific patient populations
- a. Patients with ischemic heart disease: Potent vasodilators (hydralazine, minoxidil, and dihydropyridine CCBs) may cause reflex tachycardia, thereby increasing myocardial oxygen demand; can attenuate this by also using an AV nodal depressant (β -blocker or nondihydropyridine CCB)
 - b. Elderly patients:
 - i. Caution with antihypertensive agents and orthostatic hypotension
 - ii. Initiate with low dose and titrate slowly.
 - c. African American patients: β -blockers and ACE inhibitors are generally less effective as monotherapy than in white patients; however, combination therapy with thiazides improves effectiveness; β -blockers and ACE inhibitors should still be used if comorbid conditions dictate.
 - d. Pregnant women
 - i. Methyldopa and hydralazine are recommended if a new therapy is initiated.
 - ii. Most antihypertensives (except for ACE inhibitors, ARBs, and aliskiren) can be safely continued during pregnancy.
7. Monitoring
- a. Have the patient return in 4 weeks to assess efficacy (sooner if clinically indicated).
 - b. If there is an inadequate response with the first agent (and adherence is verified) and no compelling indication exists, initiate therapy with a drug from a different class.

IV. DYSLIPIDEMIA

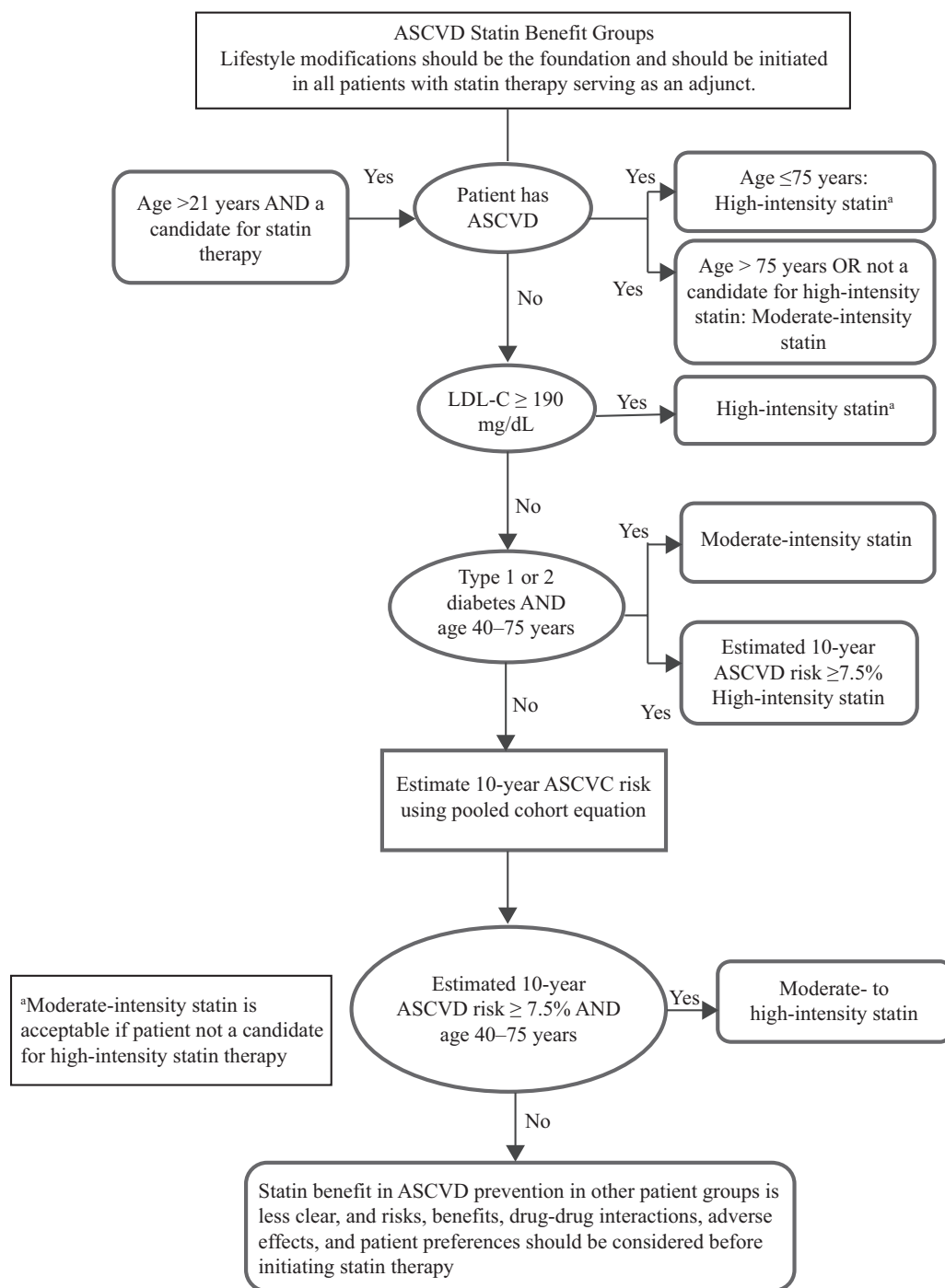
A. Primary Recommendations

1. Lifestyle modification is cornerstone of initial intervention.
 - a. Heart-healthy diet
 - b. Regular exercise
 - c. Maintain healthy weight.
 - d. Smoking cessation
2. Initiate statin therapy for secondary and primary prevention at moderate- to high-intensity doses in specific benefit groups.
 - a. Therapy no longer modified to target specific LDL-C or non-HDL-C goals
 - b. Routine initiation of statin therapy not recommended for patients with class II-IV HF or those on maintenance hemodialysis
3. Patients now placed into one of four major statin benefit groups

B. Four Major Statin Benefit Groups

1. Patients with ASCVD. Note: ASCVD includes CAD, stroke, and PAD.
2. Patients with an LDL-C of 190 mg/dL or greater
3. Patients with diabetes age 40-75 years with an LDL-C of 70-189 mg/dL and without ASCVD
4. Patients with an LDL-C of 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or greater without diabetes or ASCVD

C. Recommendations for Intensity of Statin Therapy for ASCVD Prevention



Patients 40–75 years of age without clinical ASCVD or diabetes, with an LDL-C of 70–189 mg/dL, who are not receiving statin therapy, should have their 10-year ASCVD risk recalculated every 4–6 years.

Figure 7. Statin intensity recommendations for ASCVD prevention.

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

Adapted from Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation* 2014;129(suppl 2):S1-45.

D. High-, Moderate-, and Low-Intensity Statin Doses (Table 18)

Table 18. Intensity of Statin Doses

High Intensity	Moderate Intensity	Lower Intensity
When taken daily, will lower LDL-C an average of $\geq 50\%$	When taken daily, will lower LDL-C an average of 30% to $< 50\%$	When taken daily, will lower LDL-C an average of $< 30\%$
Atorvastatin 40–80 mg Rosuvastatin 20–40 mg	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

BID = twice daily; LDL-C = low-density lipoprotein cholesterol.

Adapted from Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation* 2014(suppl 2):S1-45.

E. Risk Assessment for Primary Prevention

1. Pooled cohort equation to estimate 10-year ASCVD risk
 - a. Assists with identifying higher-risk patients for statin therapy
 - b. May be used in patients with type 1 and type 2 diabetes mellitus in primary prevention to guide the intensity of statin therapy
 - c. Should not be used for patients with clinical ASCVD or an LDL-C greater than 190 mg/dL already on statin therapy
2. 10-year ASCVD risk assessment is based on the pooled cohort equation: http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp.
 - a. Sex
 - b. Age
 - c. Race
 - d. Total cholesterol
 - e. HDL-C
 - f. Systolic BP
 - g. Treatment of high BP
 - h. Diabetes
 - i. Smoker

F. General Approach to Initiating Statin Therapy in Patients with Clinical ASCVD

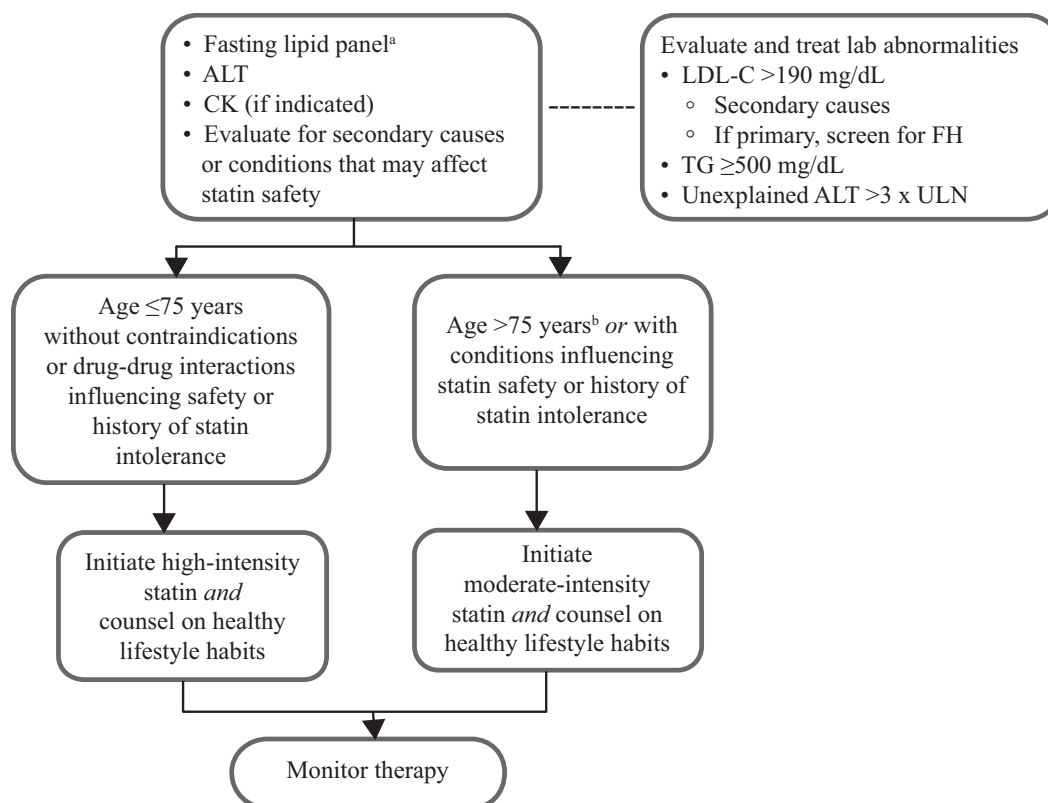


Figure 8. General approach to initiating statin therapy in patients with clinical ASCVD.

ALT = alanine aminotransferase; ASCVD = atherosclerotic cardiovascular disease; CK = creatine kinase; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; ULN = upper limit of normal. Adapted from Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation* 2014 (suppl 2):S1-45.

^aA fasting lipid panel is preferred. However, a nonfasting non-HDL-C >220 mg/dL may be indicative of a genetic hypercholesterolemia, which warrants further evaluation. If nonfasting TG ≥ 500 mg/dL, a fasting lipid panel is needed.

^bFor patients with ASCVD who are older than 75 years, it is reasonable to assess the potential for ASCVD benefits and adverse effects and to consider patient preferences in initiating moderate- to high-intensity statin therapy.

G. General Approach to Initiating Statin Therapy in Patients Without Clinical ASCVD

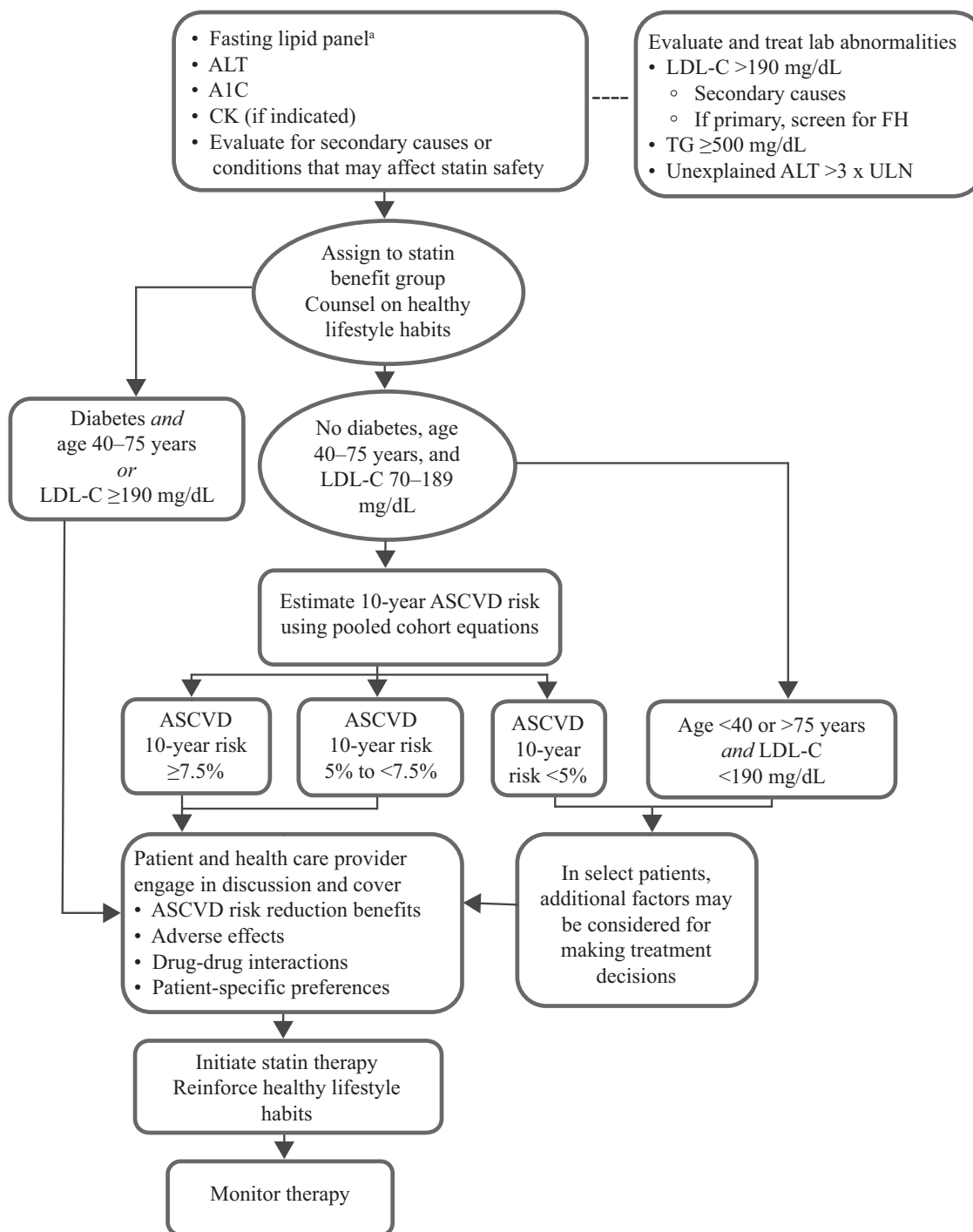


Figure 9. General approach to initiating statin therapy in patients without clinical ASCVD.

ASCVD = atherosclerotic cardiovascular disease; CK = creatine kinase; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; ULN = upper limit of normal. Adapted from Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation* 2013. Available at <http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a>.

^aA fasting lipid panel is preferred. However, a nonfasting non-HDL-C >220 mg/dL may be indicative of a genetic hypercholesterolemia, which warrants further evaluation. If nonfasting TG is ≥500 mg/dL, a fasting lipid panel is needed.

Patient Cases

8. M.M. is a 63-year-old white woman who just finished 6 months of diet and exercise for dyslipidemia. She has a history of gout, chronic nonischemic HF (LVEF 26%), diet-controlled diabetes, and asthma, as well as a 15 pack-year history of tobacco (quit 3 years ago); she drinks 3 beers a day. Because she was adopted, no family history records are available. Her medications are albuterol metered dose inhaler, lisinopril, furosemide, and Tums 2 tablets/day. Her vital signs include BP 124/80 mm Hg and HR 75 beats/minute. Her laboratory results are as follows: HDL-C 64 mg/dL, LDL-C 101 mg/dL, TG 98 mg/dL, and TC 185 mg/dL. Her pooled cohort equation estimates a 10-year ASCVD risk of 7.1%. Which is the most appropriate next step for M.M.?
- Initiate moderate-intensity statin because her 10-year risk is less than 7.5%.
 - Initiate high-intensity statin because her 10-year risk is less than 7.5%.
 - Continue lifestyle modifications and recalculate 10-year risk in 2 years.
 - Continue lifestyle modifications and do not initiate statin therapy.
9. According to the ACC/AHA blood cholesterol guidelines, which is best described as a moderate-intensity statin dose?
- Pravastatin 20 mg/day.
 - Lovastatin 20 mg/day.
 - Atorvastatin 40 mg/day.
 - Rosuvastatin 10 mg/day.

H. Management of Patients 21 Years and Older with LDL-C Greater Than 190 mg/dL

- Initiate high-intensity statin therapy to achieve at least a 50% reduction in LDL-C.
- The addition of nonstatin cholesterol-lowering agents will probably be needed.
- Should be evaluated for genetic causes
- Evaluate for secondary causes.

I. Management of Very High TG Concentrations (greater than 500 mg/dL)

- Primary goal is to prevent pancreatitis.
- Weight loss (5%–10% weight loss results in a 20% reduction in TG)
- Carbohydrates: Around 45%–50%
- Added sugars: Less than 5%
- Fructose: Less than 50 g
- Protein: 20%
- Fat: Avoid *trans* fats, saturated fats less than 5%, monounsaturated fats 1%–20%, polyunsaturated fats 10%–20%, eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) greater than 2 g.
- Exercise: Aerobic activity at least twice weekly
- Evaluate for secondary causes.
- Pharmacologic therapy (Table 20)

Table 19. Common Secondary Causes of Elevated LDL-C and TG

Cause	Increase LDL-C	Increased TG
Medications	Glucocorticoids, amiodarone, diuretics, cyclosporine	Hormone therapy, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, tamoxifen, sirolimus, atypical antipsychotics, raloxifene, β -blockers, thiazides
Dietary influences	Saturated or <i>trans</i> fats, weight gain, anorexia	Very low fat diets, high carbohydrate intake (refined), excess alcohol, weight gain
Disease states and medical conditions	Nephrotic syndrome, biliary obstruction, hypothyroidism, obesity, pregnancy	Poorly controlled diabetes, hypothyroidism, obesity, pregnancy, nephrotic syndrome, chronic renal failure, lipodystrophies

LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

Table 20. Effect of Lipid-Lowering Medications on Triglycerides

Medication	% Decrease in Triglycerides
Statins	10–30
Fibrates	30–50
Immediate-release niacin	20–50
Extended-release niacin	10–30
Ezetimibe	5–10
Omega-3 fatty acids	20–50

J. HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) Reductase Inhibitors (statins)

1. Efficacy

- a. Drugs of choice for high LDL-C or CHD risk
- b. When selecting a statin, consider the percentage of LDL-C reduction needed.
- c. Reduce LDL-C by 24%–60%.
- d. Reduce TG by 7%–40%.
- e. Raise HDL-C by 5%–15%.
- f. Reduce major coronary events.
- g. Reduce CHD mortality.
- h. Reduce coronary procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting).
- i. Reduce stroke.
- j. Reduce total mortality.

2. Mechanism of action: Inhibits enzyme responsible for converting HMG-CoA to mevalonate (rate-limiting step in production of cholesterol)

3. Main adverse effects/monitoring

- a. Myopathy (check creatine kinase [CK] at baseline and then only if muscle symptoms occur; no regular monitoring)
- b. Elevated liver enzymes
 - i. LFTs at baseline in all patients
 - ii. Perform repeat LFTs only when clinically indicated.
 - iii. Monitor for symptoms of hepatic injury.

4. Contraindications: Absolute

- a. Active liver disease, unexplained persistent elevations in hepatic transaminases

- b. Pregnancy
- c. Nursing mothers
- d. Certain medications (agent-specific; see drug interactions below)
- 5. Select drug interactions (see Table 21)
 - a. Fibrates: Increased risk of myopathy and rhabdomyolysis when coadministered with statins. Risk is greater with gemfibrozil than with fenofibrate.
 - b. Niacin: Doses greater than 1 g/day increase the risk of myopathy and rhabdomyolysis when used concomitantly with statins; risk is lower than with fibrates; statins and niacin are commonly used together; monitor for muscle pain.

Table 21. Select Drug Interactions with Statins

	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Pitavastatin	Atorvastatin	Rosuvastatin
Amiodarone	Daily dose not to exceed 40 mg		Daily dose not to exceed 20 mg				
Amlodipine			Daily dose not to exceed 20 mg				
Boceprevir, telaprevir	CI		CI			Daily dose not to exceed 40 mg (boceprevir)	
Colchicine	Use with caution	Use with caution	Use with caution	Use with caution	Use with caution	Use with caution	Use with caution
Cyclosporine	CI	Daily dose not to exceed 20 mg	CI	Daily dose not to exceed 20 mg		CI	Daily dose not to exceed 5 mg
Danazol	Daily dose not to exceed 20 mg		CI				
Diltiazem Verapamil	Daily dose not to exceed 20 mg		Daily dose not to exceed 10 mg				
Dronedarone	Daily dose not to exceed 20 mg		Daily dose not to exceed 10 mg				
Erythromycin, clarithromycin, telithromycin	CI	Daily dose not to exceed 40 mg (clarithromycin)	CI		Daily dose not to exceed 1 mg (erythromycin)	Daily dose not to exceed 20 mg (clarithromycin)	
Gemfibrozil	CI		CI	Use with caution	Use with caution		Daily dose not to exceed 10 mg
Grapefruit juice (>1 quart per day)	Avoid use		Avoid use			Avoid excess quantities (>1.2 L/day)	
Itraconazole, ketoconazole, posaconazole,	CI		CI	Daily dose not to exceed 20 mg twice daily (fluconazole)		Daily dose not to exceed 20 mg (itraconazole)	
Nefazodone	CI		CI				
Niacin	Avoid doses of niacin ≥1 g/day	Avoid doses of niacin ≥1 g/day	Avoid doses of niacin ≥1 g/day	Avoid doses of niacin ≥1 g/day	Avoid doses of niacin ≥1 g/day		Avoid doses of niacin ≥1 g/day
HIV protease inhibitors	CI		CI			CI with tipranavir plus ritonavir. Daily dose not to exceed 20 mg (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir or fosamprenavir plus ritonavir) Daily dose not to exceed 40 mg (nelfinavir)	Daily dose not to exceed 10 mg (lopinavir/ritonavir or atazanavir/ritonavir)

Table 21. Select Drug Interactions with Statins (*continued*)

	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Pitavastatin	Atorvastatin	Rosuvastatin
Ranolazine	Consider dose adjustment		Daily dose not to exceed 20 mg				
Rifampin					Daily dose not to exceed 2 mg		
Voriconazole	CI		CI				

CI = contraindicated.

Table 22. Pharmacokinetic Differences Between Statins

	Bioavailability (%)	Half-life (hours)	Elimination Metabolism	Prodrug	Solubility
Atorvastatin	12	14	3A4	No	Lipophilic
Fluvastatin	24	1	2C9	No	Hydrophilic
Lovastatin	<5	2–3	3A4	Yes	Lipophilic
Pitavastatin	51	12	2C9, 2C8	Yes	Lipophilic
Pravastatin	17	1.5–2	N/A	No	Hydrophilic
Simvastatin	<5	2	3A4	Yes	Lipophilic
Rosuvastatin	20	20	2C19	No	Hydrophilic

N/A = not applicable.

Table 23. Dosing of Statin Agents in Chronic Kidney Disease

Drug	eGFR (mL/minute)			Comments
	30–59	15–29	<15 or HD	
Atorvastatin	10–80 mg	10–80 mg	10–80 mg	
Fluvastatin	10–80 mg	10–40 mg	10–40 mg	Doses >40 mg not studied in severe renal impairment
Lovastatin	20–80 mg	10–40 mg	10–40 mg	Labeling cautions against use of doses >20 mg when CrCl < 30 mL/minute
Pitavastatin	1–2 mg	1–2 mg	1–2 mg	
Pravastatin	20–80 mg	10–40 mg	10–40 mg	Labeling recommends initial dose of 10 mg if significant renal impairment
Simvastatin ^a	20–80 mg	10–20 mg	10–20 mg	Labeling recommends initial dose of 5 mg if CrCl < 30 mL/minute
Rosuvastatin	5–40 mg	5–10 mg	— ^b	

^aThe 80-mg dose of simvastatin should be reserved for patients who have been taking simvastatin 80 mg long term (e.g., ≥12 months) and who are without evidence of muscle toxicity.

^bNo data available; cannot recommend.

CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; HD = hemodialysis.

- K. Bile Acid Sequestrants (cholestyramine, colestipol, colesevelam)
1. Efficacy
 - a. Reduce LDL-C by 15%–26%.
 - b. Raise HDL-C by 3%–6%.
 - c. May increase TG concentrations
 - d. Reduce major coronary events.
 - e. Reduce CHD mortality.
 2. Mechanism of action: Bind to bile acids to disrupt enterohepatic recirculation of bile acids. Liver is stimulated to convert hepatocellular cholesterol to bile acids.
 3. Adverse effects: GI distress, constipation
 4. Decreased absorption of other drugs: Warfarin, β -blockers, levothyroxine, and thiazides; administer drugs 1–2 hours before or 4 hours after bile acid
 5. Contraindications: Dysbetalipoproteinemia, raised TG concentrations (especially greater than 400 mg/dL)
- L. Niacin
1. Main actions
 - a. Lowers LDL-C by 15%–26%
 - b. Lowers TG by 20%–50%
 - c. Raises HDL-C by 15%–26%
 - d. Reduces major coronary events
 - e. Lowers lipoprotein (a)
 2. Mechanism of action: Inhibits mobilization of free fatty acids from peripheral adipose tissue to the liver and reduces VLDL synthesis (LDL-C and TG)
 3. Adverse effects and monitoring: Flushing, hyperglycemia, hyperuricemia, upper GI distress, increased hepatic transaminases; monitor LFTs at baseline, every 6–12 weeks, and then yearly
 4. Sustained release appears to be more hepatotoxic than other preparations (e.g., OTCs). Available as “Slo-Niacin” or twice-daily generic niacin OTC
 5. Extended release and sustained release are less likely to cause flushing.
 6. Contraindications: liver disease, severe gout, active peptic ulcer
 7. Flushing can be minimized by taking aspirin 325 mg or ibuprofen 200 mg 30–60 minutes before niacin, taking at bedtime with food, and avoiding hot beverages, spicy foods, and hot showers around the time of administration.

Table 24. Niacin Formulations

Drug Form	Brand Name	Dose Range (g)
Immediate release	Niacin	1.5–3
Immediate release	Niacor	1.5–6
Extended release	Niaspan	1–2
Sustained release	Slo-Niacin	1–2

M. Fibrates (fenofibrate, gemfibrozil)

1. Main actions
 - a. Lower LDL-C by 5%–20% (with normal TG)
 - b. May raise LDL-C by 45% (with very high TG)
 - c. Lower TG by 30%–55%
 - d. Raise HDL-C by 18%–22%
 - e. Reduce progression of coronary lesions
2. Mechanism of action: Reduces rate of lipogenesis in the liver
3. Adverse effects and monitoring: Dyspepsia, gallstones, myopathy, increased hepatic transaminases; monitor LFTs every 3 months during first year and then periodically
4. Contraindications: Severe renal or hepatic disease

N. Ezetimibe

1. Efficacy
 - a. Lowers LDL-C by 18%–20%
 - b. May raise HDL-C by 1%–5%
 - c. Lowers TG by 5-10%
2. Mechanism of action: Inhibition of cholesterol absorption
3. Adverse effects: Headache, rash; no monitoring necessary, except LFTs when coadministered with statins
4. Adjunctive therapy to statin
5. Recent data suggest that combination with simvastatin is superior than simvastatin alone in reducing CV events.

Patient Case

10. Which best describes a potential secondary cause of high TGs?

- A. Amiodarone.
- B. Biliary obstruction.
- C. Sirolimus.
- D. Saturated fats.

O. Omega-3-Acid Ethyl Esters (Lovaza)

1. Efficacy
 - a. Lowers TG by 26%–45%
 - b. May raise LDL-C to 45% when TG concentrations are very high
 - c. Raises HDL-C by 11%–14%
2. Mechanism of action: Unknown. Possible inhibition of acyl coenzyme A:1,2 diacylglycerol acyltransferase, increased hepatic β -oxidation, or reduction in TG hepatic synthesis
3. Adverse effects: GI (e.g., burping, taste perversion, dyspepsia); at more than 3 g/day, inhibition of platelet aggregation, bleeding
4. Used to treat hypertriglyceridemia as an adjunct to diet in adults with TG concentrations of ≥ 500 mg/dL
5. Dose: 4 g/day as a single dose or in two divided doses

- P. Icosapent Ethyl (Vascepa)
1. Efficacy
 - a. Lowers TG 33%
 - b. Does not appear to raise LDL-C
 2. Mechanism of action: It is suggested that EPA, the active metabolite of icosapent ethyl, reduces hepatic VLDL-TG synthesis and secretion and increases TG clearance from circulating VLDL particles.
 3. Adverse effects: arthralgia
 4. Used to treat hypertriglyceridemia (≥ 500 mg/dL) as an adjunct to diet
 5. Dose: 2 g twice daily with food
- Q. Omega-3-Carboxylic Acid (Epanova)
1. Efficacy
 - a. Lowers TG 30%
 - b. May raise HDL-C by 5%
 - c. May raise LDL-C by 25%
 2. Mechanism of action: Not fully understood
 3. Adverse effects: diarrhea
 4. Used to treat hypertriglyceridemia (≥ 500 mg/dL) as an adjunct to diet
 5. Dose: 2 g (2 capsules) or 4 g (4 capsules) once daily
- R. Lomitapide (Juxtapid)
1. Efficacy: Lowers LDL-C by about 40%
 2. Mechanism of action: A selective microsomal triglyceride protein inhibitor
 3. Indicated for homozygous familial hypercholesterolemia (HoFH)
 4. Adverse effects: Elevated LFTs, GI symptoms
 5. Available only through the Risk Evaluation and Mitigation Strategy (REMS) program
 6. Dose: 5 mg once daily
- S. Mipomersen (Kynamro)
1. Efficacy: Additional 25% reduction in LDL-C
 2. Mechanism of action: Oligonucleotide targeted to human messenger RNA
 3. Indicated for HoFH
 4. Adverse effects: Elevated LFTs, flulike symptoms
 5. Available only through the REMS program
 6. Dose: 200 mg subcutaneously once weekly

V. CHRONIC CORONARY HEART DISEASE AND CHRONIC STABLE ANGINA

Coronary heart disease (CHD) is a general term that does not discriminate between the various phases the individual may cycle between for several decades. These phases include asymptomatic disease, stable angina, progressive angina, unstable angina, non-ST-segment elevation MI, and ST-segment elevation MI.

Depending on the patient's manifestations, some therapies may be added or modified. However, several basic treatment rules apply to all individuals with CHD, regardless of the symptoms they may experience.

The following mnemonic, developed for patients with chronic stable angina, can be applied to all patients with CHD.

- A = Aspirin and Antianginal Therapy
- B = β -Blocker and BP
- C = Cigarette Smoking and Cholesterol
- D = Diet and Diabetes
- E = Education and Exercise

Although not all patients with CHD have diabetes or smoke cigarettes, the mnemonic is a way to remember the primary areas that should be addressed, as applicable, in all patients with CHD.

Some important recommendations:

- Weight reduction/maintenance to a body mass index of 18.5–24.9 kg/m² and a waist circumference less than 40 inches for a male and less than 35 inches for a female
- Physical activity for 30–60 minutes/day 7 days/week (minimum of 5 days/week)
- LDL-C less than 100 mg/dL
- BP less than 140/90 mm Hg
- Alcohol consumption should be limited to 1 drink (4 oz of wine, 12 oz of beer, or 1 oz of spirits) per day for women and 1 or 2 drinks per day for men.
- No smoking and no environmental exposure to smoke
- Reduced intake of saturated fats (to less than 7% of total calories), trans-fatty acids (to less than 1% of total calories), and cholesterol (to less than 200 mg/day)
- If patient has diabetes, glycosylated hemoglobin less than 7%; a goal A1C of 7%–9% is reasonable in certain patients (avoid rosiglitazone)
- Annual influenza vaccine

Therapeutic Management of CHD

A. Antiplatelet Therapy

1. Aspirin
 - a. Indicated in all patients with CHD unless contraindicated
 - b. Dose: 75–162 mg/day
 - c. Decreases CV events by about one-third
2. Clopidogrel
 - a. A dose of 75 mg/day if aspirin absolutely contraindicated
 - b. Use in combination with aspirin 75–162 mg may be reasonable in certain high-risk patients.
3. Dipyridamole
 - a. Should be avoided in symptomatic CHD
 - b. Increases exercise-induced myocardial ischemia
 - c. No benefit over aspirin in the absence of symptomatic CHD

B. Lipid-Lowering Therapy (see section IV: Dyslipidemia)

1. Counsel on healthy lifestyle habits
2. Fasting lipid panel, ALT, CK, consider secondary causes of dyslipidemia, evaluate for conditions that may influence statin safety

3. If LDL-C greater than 190 mg/dL, evaluate for secondary causes; if primary, screen family for familial hypercholesterolemia.
 4. If TG are 500 mg/dL or greater, ensure fasting lipid panel, screen for secondary causes, employ lifestyle modifications, consider secondary causes, and consider pharmacologic therapy.
 5. High-intensity statin therapy if without contraindications, drug-drug interactions, or history of statin intolerance
- C. ACE Inhibitors
1. ACE inhibitors greatly decrease CV events in patients with CHD (and no LV dysfunction) at high risk of subsequent CV events.
 2. Should be considered in all patients who also have an LVEF of 40% or less, HTN, diabetes mellitus, and/or CKD
 3. Consider using in lower-risk patients with a mildly reduced or normal LVEF in whom CV risk factors are well controlled and revascularization has been performed.
 4. Postulated mechanisms: Plaque stabilization
- D. ARBs: Recommended as an alternative to ACE inhibitors in patients who also have an LVEF of 40% or less, HTN, diabetes mellitus, and/or CKD or who are unable to tolerate an ACE inhibitor (e.g., cough or angioedema)
- E. Additional Therapies for Chronic Stable Angina
1. Definition: Predictable angina symptoms with exertion
 2. Goals: Reduce symptoms of ischemia, increase physical function, and improve quality of life. In general, achieved by either decreasing myocardial oxygen demand or increasing myocardial oxygen supply
 3. Specific agents
 - a. β -Blockers
 - i. Pharmacologic effects: Decreased inotropy and HR (decrease oxygen demand)
 - ii. Goal resting HR 55–60 beats/minute (less than 50 beats/minute if angina symptoms continue)
 - iii. May be considered chronic therapy for all patients with coronary or other vascular disease
 - iv. Goal exercise HR of no more than 75% HR associated with angina symptoms
 - v. Contraindications: Severe bradycardia (HR less than 50 beats/minute), high-degree AV block (without pacemaker), sick sinus syndrome (without pacemaker)
 - b. Calcium channel blockers
 - i. Pharmacologic effects
 - (a) Decrease coronary vascular resistance and increase coronary blood flow (increase oxygen supply)
 - (b) Negative inotropy, to varying degrees; nifedipine much greater than amlodipine and felodipine (decrease oxygen demand)
 - (c) Decrease HR (verapamil and diltiazem only) (decrease oxygen demand)
 - ii. Place in therapy
 - (a) A scheduled nitrate is useful in conjunction with a β -blocker or non-dihydropyridine CCB (blunt the reflex sympathetic tone with nitrate therapy).
 - (b) As-needed sublingual tablets or spray nitrate is necessary to relieve effort or rest angina.
 - (c) In addition, as-needed nitrates can be used before exercise to avoid ischemic episodes.
 - iii. Contraindications: Hypertrophic obstructive cardiomyopathy, inferior wall MI, severe aortic valve stenosis, sildenafil and vardenafil within 24 hours, tadalafil within 48 hours

- c. Nitrates
 - i. Pharmacologic effects:
 - (a) Endothelium-dependent vasodilation, dilates epicardial arteries and collateral vessels (increase oxygen supply)
 - (b) Decreased LV volume because of decreased preload mediated by venodilation (decrease oxygen demand)
 - ii. Place in therapy
 - (a) A scheduled nitrate is useful in conjunction with a β -blocker or non-dihydropyridine CCB (blunt the reflex sympathetic tone with nitrate therapy).
 - (b) As-needed sublingual tablets or spray nitrate is necessary to relieve effort or rest angina.
 - (c) In addition, as-needed nitrates can be used before exercise to avoid ischemic episodes.
 - iii. Contraindications: Hypertrophic obstructive cardiomyopathy, inferior wall MI, severe aortic valve stenosis, sildenafil and vardenafil within 24 hours, tadalafil within 48 hours
- d. Ranolazine
 - i. Pharmacologic effects
 - (a) Inhibits the late phase of the inward sodium channel in ischemic myocytes during repolarization leading to a reduction in intracellular sodium concentrations. This reduction in sodium concentrations leads to reduced calcium influx which decreases reduces ventricular tension and myocardial oxygen consumption.
 - (b) Increases “oxygen efficiency”
 - ii. Place in therapy
 - (a) Ideal role is unclear. Currently, as a substitute for a β -blocker if initial treatment with β -blockers results in adverse effects or if β -blockers are ineffective or contraindicated
 - (b) Use in combination with β -blockers, CCBs, or nitrates when initial management with these drugs is unsuccessful.
 - (c) Important points
 - (1) No significant effects on HR or BP; thus, bradycardia and hypotension are not of concern
 - (2) Dose-related QT prolongation
 - (3) Metabolized by CYP3A
 - (A) Avoid in hepatic dysfunction.
 - (B) Avoid use with strong CYP3A inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir.
 - (C) Avoid use with CYP3A inducers such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, and carbamazepine, as well as with St. John’s wort.
 - (D) Limit the dose of simvastatin to 20 mg daily when administered with ranolazine.
 - (E) Limit the dose to 500 mg twice daily in patients receiving moderate CYP3A4 inhibitors, including diltiazem, verapamil, erythromycin, and fluconazole, and in those receiving grapefruit juice.

REFERENCES

Heart Failure

1. Amabile CM, Spencer AP. Keep your heart failure patient safe: a review of potentially dangerous medications. *Arch Intern Med* 2004;164:709-20.
2. Jackevicius CA, Page RL, Chow S, et al. High impact articles related to the management of heart failure: 2008 update. *Pharmacotherapy* 2009;29:82-120.
3. Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail* 2010;16:e1-194.
4. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;128:e240-327.

Atrial Fibrillation

1. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/HRS and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:1916-26.
2. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130(23):2071-104.
3. You JJ, Singer DE, Howard P, et al. Anti-thrombotic therapy in atrial fibrillation. *Chest* 2012;141(suppl):e531S-75S.
4. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-33.

Hypertension

1. Appel LJ, Brands MW, Daniels SR, et al. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension* 2006;47:296-308.
2. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Coll Cardiol* 2011;57:2037-114.
3. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
4. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2014;37:S14-80.
5. Flack JM, Sica DA, Bakris G, et al. International Society on Hypertension in Blacks. Management of high blood pressure in blacks: an update of the International Society on Hypertension in Blacks Consensus Statement. *Hypertension* 2010;56:780-800.
6. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC8). *JAMA* 2014;311(5):507-20.
7. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2012;2:339.
8. Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2007;115:2761-88.

9. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. A statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens* 2014;16:14-26.
10. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;128:e240-327.

Dyslipidemia

1. Grundy SM, Cleeman JI, Baird-Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.
2. Kastelein JJP, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;358:1431-43.
3. National Institutes of Health National Heart Lung and Blood Institute. Third report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
4. Pasternak RC, Smith SC, Baird-Merz CN, et al. ACC/AHA/NHLBI advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
5. Stone NJ, Robinson J, Liechtenstein HA, et al. 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(suppl 2):S1-45.

CHD and Chronic Stable Angina

1. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACCF/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2014;130:1749-1767.
2. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. *Angiography and Interventions, and Society of Thoracic Surgeons Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Guidelines, and the American College of Physicians, American Association for Thoracic College of Cardiology Foundation/American Heart Association Task Force on Practice Management of Patients With Stable Ischemic Heart Disease. Circulation* 2012;126:3097-137.
3. Gibbons RJ, Abrams J, Chatterjee K, et al. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *Circulation* 2007;116:2762-72.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

This patient has significant systolic dysfunction with an LVEF of 20%, NYHA class III. At this time, the best option is to increase her carvedilol dose to the goal dose of 25 mg twice daily (Answer A). Despite her HR of 68 beats/minute, it is safe to increase the β -blocker. Higher doses of carvedilol have been associated with greater reductions in mortality, whereas increases in ACE inhibitors have not shown additional reductions in mortality. Appropriate monitoring would include signs and symptoms of hypotension and bradycardia. Her ACE inhibitor is already at the target dose; therefore, it should be increased to the maximal dose only if there is another indication to do so (HTN or proteinuria) (Answer B). Spironolactone 25 mg/day is the recommended dose for patients with systolic dysfunction who are already receiving an ARB and a β -blocker and are NYHA class III. Increasing the dose of spironolactone to 50 mg/day is unwarranted (Answer C). Her digoxin concentration of 0.7 ng/dL is within the desired range of 0.7–0.9 ng/mL, so no dosage increase is warranted because this would not improve efficacy and would only increase the risk of toxicity (Answer D).

2. Answer: B

Increasing the ACE inhibitor to target doses should be achieved in all patients, if possible. This patient's BP of 120/70 mm Hg safely permits increasing enalapril from 5 to 10 mg twice daily, making Answer B correct. There is no consensus that carvedilol is preferred to extended-release metoprolol for patients with HF (Answer A). Spironolactone is not appropriate to initiate in this patient because his baseline SCr concentration is greater than 2.5 mg/dL (Answer C). Digoxin should be added only in patients who continue to have symptoms or hospitalizations despite optimal therapy with an ACE inhibitor, β -blocker, and diuretic; this patient's ACE inhibitor therapy is not considered optimal at this time (Answer D).

3. Answer: C

Cilostazol, a phosphodiesterase type-3 inhibitor, may be associated with an elevated risk of ventricular arrhythmias and death in patients with HF (Answer C). Acetaminophen is the drug of choice for mild to moderate pain in patients with HF because NSAIDs can

lead to water retention and worsening HF symptoms (Answer A). The selective serotonin reuptake inhibitors are not contraindicated in HF (Answer B). Properly dosed thyroid replacement therapy, as evidenced by his therapeutic thyroid-stimulating hormone concentration, is also beneficial because both hypothyroidism and hyperthyroidism have negative consequences in patients with HF (Answer D).

4. Answer: D

This patient's ventricular rate is well controlled with his metoprolol tartrate therapy; therefore, no additional AV node blockade is warranted with either a nondihydropyridine CCB (Answer B) or digoxin (Answer A). This patient with AF would be considered at high risk of a stroke because of his history of HTN and TIA. Given these risk factors, this patient has a CHADS₂VASc score of 3, so anticoagulation with warfarin titrated to a goal INR of 2.5 is indicated (Answer C). However, the 2012 CHEST supplement now recommends dabigatran over warfarin. In addition, this patient may be unable to travel to his primary care provider's office for weekly INR checks. In this case, dabigatran 150 mg twice daily (Answer D) may be the best choice because it does not warrant INR monitoring, the patient has prescription insurance, he appears to be adherent to a twice-daily medication regimen already, and he does not have renal dysfunction.

5. Answer: C

With the new diagnosis of HF, this patient can no longer receive sotalol. Discontinuing this medication is very important so that his risk of arrhythmic death is not increased. Adding metoprolol is a reasonable approach but not until his HF has been properly controlled, making both Answer A and Answer D incorrect. If rhythm control is desired, amiodarone and dofetilide are the only two drugs that have been proven safe and effective in patients with HRrEF, making Answer C correct. Of importance, drug interactions exist between amiodarone, digoxin, and warfarin, which will need to be addressed. Dronedarone (Answer B) is not recommended in patients with symptomatic HF with a recent decompensation.

6. Answer: B

With his history of MI, this patient has a goal BP of less than 140/90 mm Hg and a compelling reason to have a β -blocker as part of his antihypertensive regimen. In general, African Americans do not respond as well as white patients to the antihypertensive effects of β -blockade; however, β -blockers should still be used in this population, especially in the presence of a compelling indication. Maintaining his regimen of hydrochlorothiazide increases the likelihood of adequate BP control because African Americans typically respond well to diuretic therapy, bearing in mind that most people require two or more drugs to attain adequate BP control (Answer B). The regimens without a β -blocker are inappropriate because of the patient's medical history of an acute MI. Therapy consisting of losartan (Answer C and Answer D) or diltiazem (Answer A) is inferior to β -blockade in this patient population.

7. Answer: C

The BP target in younger people with diabetes mellitus can be lower than 130/80 mm Hg if treatment does not present a burden to the patient. The presence of diabetes is a compelling reason to include an ACE inhibitor in the absence of any contraindication. Lisinopril initiated at a low dose of 2.5 mg/day is appropriate given this patient's level of renal dysfunction and mildly elevated BP (Answer C). Although amlodipine (Answer B) could get the patient to her goal BP, this agent might not be as renal-protective as an ACE inhibitor. Likewise, no compelling indication is present for using a β -blocker in this patient; therefore, an atenolol-based regimen (Answer D) is less desirable than the ACE inhibitor regimen. In all situations, lifestyle modifications should be emphasized to this patient (Answer A); however, additional drug therapy is warranted for her.

8. Answer: A

This patient falls into one of the four statin benefit groups and therefore should be initiated on statin therapy, making Answer D incorrect. This patient would be a candidate for moderate-intensity statin therapy because she has diabetes (Answer A), and her 10-year risk is 7.5% or less. Because she falls into one of the statin benefit groups, recalculating her risk in 2 years would not be appropriate (Answer C). Because she has a 10-year risk of 7.5% or less, she is not a candidate for a high-intensity statin (Answer B), despite having

diabetes. If she did not have diabetes, her 10-year risk would be only 3%, and statin therapy could be discussed as a potential option; moreover, perhaps based on the physician and patient discussion, statin therapy could be deferred and her risk recalculated in 4–6 years.

9. Answer: D

A moderate-intensity statin dose should provide a reduction in LDL-C of 30% to 50%. Pravastatin 20 mg (Answer A) and lovastatin 20 mg (Answer B) are considered low-intensity statins because they will lower LDL-C by less than 30%. Atorvastatin 40 mg is considered a high-intensity statin because it will lower LDL-C by more than 50% (Answer C). Rosuvastatin 10 mg will reduce LDL-C between 30% and 50%; therefore, it is considered a moderate-intensity statin (Answer D).

10. Answer: C

If fasting TGs are 500 mg/dL or greater or if LDL-C is greater than 190 mg/dL, patients should be assessed for potential secondary causes of their dyslipidemia. In addition, patients with an LDL-C greater than 190 mg/dL should be evaluated for familial hypercholesterolemia, as should their family members. Secondary causes of elevated TG include high intake of carbohydrates, excessive alcohol intake, oral estrogens, glucocorticoids, protease inhibitors, sirolimus (Answer C), thiazides, anabolic steroids, raloxifene, β -blockers, nephrotic syndrome, chronic renal failure, lipodystrophies, poorly controlled diabetes, hypothyroidism, pregnancy, and obesity. Amiodarone (Answer A), biliary obstruction, and saturated fats (Answer D) are all secondary causes of increased LDL-C.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

This patient has LV systolic dysfunction (NYHA class III), probably secondary to her MI 4 months ago, and is not on optimal HF therapy with ACE inhibitors and β -blockers, making Answer A incorrect. ACE inhibitors are considered the cornerstone of therapy for LV systolic dysfunction according to evidence that they slow the progression of HF and reduce symptoms, hospitalizations, and mortality in this patient population. ACE inhibitors should be initiated in all patients with LV systolic dysfunction. This patient has no contraindications for using an ACE inhibitor; therefore, lisinopril should be initiated (Answer D). Digoxin is not indicated unless a patient is symptomatic on optimal HF therapy (Answer B). This patient is neither symptomatic nor on optimal therapy. Even though the patient is NYHA class III, no rationale exists for adding spironolactone at this time because she is not on optimal HF therapy (Answer C).

2. Answer: C

This patient is taking the target dose of enalapril; further increases in the enalapril dose are unnecessary unless the patient is hypertensive (Answer B). Compared with lower doses, higher doses of ACE inhibitors do not provide an additional reduction in all-cause or CV mortality. The addition of β -blocker therapy, initially at a low dose, together with ACE inhibitor therapy, is recommended for further reductions in morbidity and mortality and for slowing the progression of HF (Answer C). Digoxin is indicated only in symptomatic patients, despite optimal therapy, and this patient's pharmacotherapy has not been optimized, making Answer A and Answer D incorrect.

3. Answer: A

This patient has diastolic dysfunction, which is a problem with ventricular relaxation. The preferred therapy is either a β -blocker or a nondihydropyridine CCB, each of which slows the HR and permits the ventricle greater time to fill with blood. Diltiazem, a nondihydropyridine CCB, would be appropriate to initiate in this patient. Nifedipine can cause reflex tachycardia, which potentiates diastolic dysfunction by reducing ventricular filling time; therefore, this drug should be discontinued (Answer A). Diuretics should be used cautiously

because patients with diastolic dysfunction are often fluid-dependent (preload) for maximal ventricular filling. In addition, this patient has no symptoms of systemic congestion, suggesting a need for increased diuresis, making Answer B incorrect. Digoxin has no role in managing diastolic dysfunction (Answer C). Although ACE inhibitors are first-line therapy for LV systolic dysfunction, they can be considered in diastolic dysfunction if further antihypertensive therapies are needed after the HR is decreased (Answer D).

4. Answer: D

This patient has a CHA₂DS₂-VASc score of 4 (risk factors are HTN, PAD, and age older than 75), making him a candidate for warfarin therapy because of his AF. This will greatly decrease his risk of stroke from about 5% per year to about 1% per year. Because his HR is less than 80 beats/minute with atenolol therapy, there is no reason to discontinue atenolol, nor is there reason to add an additional rate control drug such as digoxin (Answer B) or diltiazem (Answer A). With his PAD, atorvastatin therapy is necessary, and his BP is well controlled; therefore, increasing the lisinopril dose is not warranted, making Answer A and Answer C incorrect. To derive the beneficial antiplatelet effects for CV event prevention, aspirin 81 mg is adequate. Aspirin 325 mg is also effective but has a greater risk of bleeding with concomitant warfarin. Therefore, adding warfarin and decreasing the dose of aspirin to 81 mg/day (Answer D) is correct.

5. Answer: A

This patient is experiencing a rapid ventricular response with exercise or strenuous activity, causing the sensation of palpitations and dyspnea. Digoxin alone poorly controls the ventricular rate during times of high sympathetic influence (e.g., exercise). Additional therapy is usually necessary to control the ventricular rate adequately. A β -blocker such as metoprolol succinate is a good choice to maintain HR during activity (Answer A). Using verapamil with digoxin in this patient could result in signs or symptoms of toxicity, given his current digoxin concentration. In addition, he is already taking a CCB, making verapamil not a good choice (Answer D). The subsequent digoxin concentration may cause symptoms of toxicity. Similarly, doubling the digoxin

dose would almost double the current serum concentration to 2.2 ng/dL, which should be avoided (Answer B). Instructing the patient to avoid activity is undesirable because physical activity should be encouraged and supported in all patients, especially in those with risk factors for CV disease (Answer C).

6. Answer: D

This patient's systolic BP goal is 140–145 mm Hg. Given that he is already taking two medications to control his BP, further intensification to a systolic BP of less than 140 mm Hg could be considered, but given his age (82) and his systolic BP (145 mm Hg), the patient is within goal (Answer D). He has already reached a systolic BP goal of less than 150 mm Hg, making Answer A incorrect. Decreasing his BP to less than 130 mm Hg would not be appropriate for an older adult; therefore, Answer B is incorrect. In addition, increasing lisinopril from 40 to 80 mg is unlikely to achieve a significant degree of BP lowering. Given that the patient is tolerating his two-drug regimen to treat his HTN, adding a third agent to only slightly lower his BP to less than 140 mm Hg is probably not worth the risk of the patient's experiencing negative effects from the medication; therefore, Answer C is incorrect.

7. Answer: D

This patient has been identified as being at risk of ASCVD according to his pooled cohort equation result of 14.6%. Therefore, the patient falls into one of the four benefit groups (age 40–75 years and 10-year ASCVD risk of 7.5% or greater) and thus should be initiated on statin therapy. According to the guidelines, this patient should be treated with moderate- to high-intensity statin therapy. Although simvastatin 20 mg is considered a moderate-intensity dose, adding gemfibrozil to this patient's regimen would be inappropriate because gemfibrozil is contraindicated in combination with simvastatin; also, his TGs are less than 500 mg/dL and need not be specifically targeted (Answer A). Using pravastatin 20 mg would be inappropriate because this is considered a low-intensity dose, and it would not provide the more than 30%–50% reduction in LDL-C that is recommended. In addition, fenofibrate would not be needed at this time because his TG levels are lower than 500 mg/dL (Answer C). Although rosuvastatin 5 mg is a typical starting dose of this medication, it is not a moderate- to high-intensity dose and would not be

appropriate (Answer B). Atorvastatin 40 mg is considered a high-intensity dose, and it will provide a greater than 50% reduction in LDL-C, as is recommended (Answer D).

8. Answer: D

This patient has a calculated 10-year ASCVD risk of 3.9%. Therefore, he does not fall into one of the statin benefit groups. Thus, statin therapy at any intensity, moderate (Answer C) or high (Answer A), would be inappropriate at this time. According to the cholesterol guidelines, patients who are between 40 and 75 years of age, without ASCVD or diabetes, and with an LDL-C between 70 and 189 mg/dL should have their 10-year risk score recalculated every 4–6 years, making Answer D correct and Answer B incorrect.

9. Answer: D

Secondary causes of hypertriglyceridemia should be ruled out when TG levels are greater than 500 mg/dL or when LDL-C is greater than 190 mg/dL. Different medications, conditions, and diet can affect these lipid parameters. Although obesity, poorly controlled diabetes, olanzapine, and metoprolol can increase TG levels, coenzyme Q does not affect TG; therefore, Answer A is incorrect. Alcohol consumption, poorly controlled diabetes, and β -blockers can all increase TG, but weight loss does not increase TG. However, weight loss can lower LDL-C and TG; therefore, Answer B is incorrect. All the choices in Answer C can increase TG, except for biliary obstruction, which can lead to increased LDL-C, making this an incorrect choice. All of the conditions, medications, or disease states in Answer D can increase TG, making this option correct.