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 who are 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 and the appropriate intensity of statin therapy when applicable.
5. Determine the appropriate pharmacologic therapy for patients with stable coronary heart disease.

Abbreviations in This Chapter

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACC/AHA</td>
<td>American College of Cardiology/ American Heart Association</td>
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<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
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<tr>
<td>ARA</td>
<td>Aldosterone receptor antagonist</td>
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<tr>
<td>ARB</td>
<td>Angiotensin II receptor blocker</td>
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<tr>
<td>ASCVD</td>
<td>Atherosclerotic cardiovascular disease</td>
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<tr>
<td>AV</td>
<td>Atrioventricular</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CCB</td>
<td>Calcium channel blocker</td>
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<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>CO</td>
<td>Cardiac output</td>
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<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
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<tr>
<td>DASH</td>
<td>Dietary Approaches to Stop Hypertension</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>DHA</td>
<td>Docosahexaenoic acid</td>
</tr>
<tr>
<td>DHP</td>
<td>Dihydropyridine</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>HDL-C</td>
<td>High-density lipoprotein-cholesterol</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failures</td>
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<tr>
<td>HFpEF</td>
<td>Heart failure with preserved ejection fraction</td>
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<tr>
<td>HoFH</td>
<td>Homozygous familial hypercholesterolemia</td>
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<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
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<tr>
<td>INR</td>
<td>International normalized ratio</td>
</tr>
<tr>
<td>K</td>
<td>Potassium</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein-cholesterol</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Na</td>
<td>Sodium</td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drug</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>P-gp</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>REMS</td>
<td>Risk Evaluation and Mitigation Strategy</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>Scr</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>SR</td>
<td>Sinus rhythm</td>
</tr>
<tr>
<td>SVR</td>
<td>Systemic vascular resistance</td>
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<tr>
<td>TC</td>
<td>Total cholesterol</td>
</tr>
<tr>
<td>TEE</td>
<td>Transesophageal echocardiogram</td>
</tr>
<tr>
<td>TG</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
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</table>

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 a follow-up. She 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 atorvastatin 40 mg every night. Her vital signs include blood pressure (BP) 138/80 mm Hg and heart rate (HR) 58 beats/minute. Her lungs are clear, and laboratory results are within normal limits. Given her history and physical examination, what is the most appropriate modification to R.S.’s current drug therapy?

   A. Continue current therapy.
   B. Initiate digoxin 0.125 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 a follow-up. She is euvoletic. 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. What is the best way to 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 furosemide 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 furosemide 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 asymptomatic 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 dyslipidemia. 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 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. His international normalized ratio (INR) is 2.4, and his digoxin concentration is 1.1 ng/mL. All other laboratory results are within normal limits. 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. Add verapamil 240 mg/day.
   D. Continue current regimen and advise the patient to avoid activities that cause signs or symptoms.

6. R.P. is an 82-year-old African American man with a history of HTN 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. His laboratory values are normal. Which is the best therapy for R.P.?
   A. Add hydrochlorothiazide 25 mg/day to achieve a systolic blood pressure (SBP) goal of less than 140 mm Hg.
   B. Increase lisinopril to 80 mg/day and titrate to achieve an SBP goal of less than 130 mm Hg.
   C. Add atenolol 50 mg/day to achieve an SBP less than 140 mm Hg.
   D. Make no changes to his current medications because his SBP 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 atherosclerotic cardiovascular disease (ASCVD) risk of 14.6%. Which would be the best pharmacologic therapy to initiate in J.T.?
   
   A. Initiate simvastatin 20 mg/day and gemfibrozil 600 mg twice daily.
   
   B. Initiate rosuvastatin 2.5 mg/day.
   
   C. Initiate pravastatin 20 mg/day and fenofibrate 160 mg/day.
   
   D. Initiate atorvastatin 40 mg/day.

8. J.S. is a 43-year-old man with HTN who presents for an annual physical examination. His family history is significant for his father having CHD. His only medication is lisinopril 10 mg/day. His BP is 145/90 mm Hg. A fasting lipid profile shows TC 238 mg/dL, TG 95 mg/dL, LDL-C 176 mg/dL, and HDL-C 43 mg/dL. His calculated 10-year ASCVD risk according to the pooled cohort equation is 3.9%. 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 (height 70 inches, weight 135 kg [1 month ago 143 kg]) with a history of diabetes mellitus (DM), chronic kidney disease, 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 (SCr) 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. His other laboratory values are within normal limits. Which best describes potential secondary causes of elevated TG concentrations 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.
   
   D. Alcohol consumption, obesity, poorly controlled diabetes, olanzapine, metoprolol.

Questions 10 and 11 pertain to the following case.
A.M. is a 32-year-old woman with type 1 DM and HTN. Her current medication regimen is as follows: ramipril 10 mg/day, chlorothalidone 25 mg/day, amlopidine 10 mg/day, ethinyl estradiol 20 mcg/norethindrone 1 mg (for the past 2 years), and insulin as directed. Her vital signs today include BP 145/83 mm Hg, repeated BP 145/81 mm Hg; HR 82 beats/minute; height 66 inches; weight 70 kg. A.M. would prefer not to take any more drugs, if possible.

10. Which option is the best clinical plan for A.M.?
   
   A. No change in therapy is currently warranted.
   
   B. Advise weight loss and recheck her BP in 3 months.
   
   C. Change chlorothalidone to hydrochlorothiazide.
   
   D. Discuss changing her contraceptive method.

11. A.M. and her husband have decided they are ready to have children. What is the best medication option for A.M.?
   
   A. No change in therapy is warranted.
   
   B. Discontinue ramipril and replace with labetalol.
   
   C. Increase chlorothalidone to 50 mg/day.
   
   D. Discontinue all antihypertensive therapy.
12. A 66-year-old African American man (height 70 inches, weight 91 kg) with AF and CHD (non-ST-segment elevation MI and stent placement 3 years ago) presents with palpitations. Rate control therapy, including trials of β-blockers and non-dihydropyridine calcium channel blockers, has been unsuccessful in controlling his symptoms. He currently takes metoprolol succinate 50 mg/day, aspirin 81 mg/day, atorvastatin 80 mg/day, lisinopril 5 mg/day, and warfarin 4 mg/day. His laboratory results show INR 2.2, potassium 4.8 mEq/L, SCr 1.2 mg/dL. His BP is 110/70 mm Hg, and his HR is 95 beats/minute. Which is the best antiarrhythmic therapy for him?
   A. Disopyramide.
   B. Flecainide.
   C. Propafenone.
   D. Sotalol.
BPS Pharmacotherapy Specialty Examination Content Outline
This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:
1. Domain 1: Patient-specific pharmacotherapy
   a. Task 1: 1–8, 10, 11, 12, 13, 14, 17
   b. Task 2: 1–3
   c. Task 3: 1–2
   d. Task 4: 1–7
   e. Task 5: 1–3
   f. Systems and patient-care problems
      i. Atrial fibrillation
      ii. Chronic CHD and chronic stable angina
      iii. Heart failure
      iv. Hypertension
      v. Dyslipidemia
2. Domain 2: Retrieval, generation, interpretation, and dissemination of knowledge in pharmacotherapy, Task 2, Knowledge Statements 1–5
3. Domain 3: System and population-based pharmacotherapy, Task 2, Knowledge Statements 4–5
I. HEART FAILURE

Patient Cases
1. L.S. is a 48-year-old woman with alcohol-induced cardiomyopathy. Her most recent LVEF is 20%; her daily activities are limited by dyspnea and fatigue (NYHA class III). Her medications include lisinopril 40 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 12 mg/dL, SCr 0.8 mg/dL, glucose 98 mg/dL, calcium 9.0 mg/dL, phosphorus 2.8 mg/dL, magnesium 2.0 mEq/L, and digoxin 0.7 ng/mL. She weighs 69 kg, and her vital signs include blood pressure (BP) 112/70 mm Hg and heart rate (HR) 68 beats/minute. She has normal breath sounds and no pedal edema. What is the best approach for maximizing the management of her HF?
   A. Increase carvedilol to 25 mg twice daily.
   B. Increase lisinopril to 80 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 CHD (MI 3 years ago), HTN, depression, chronic kidney disease (CKD; baseline SCr 2.8 mg/dL), 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. What 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.

A. Background: HF 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. Prevalence
      a. Affects 5.1 million Americans
      b. Prevalence increases with age
   2. Heart failure with reduced ejection fraction (HFrEF) 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 chronic heart disease (CHD).
      d. One third of cases are attributable to nonischemic cardiomyopathy.
         i. HTN
         ii. Thyroid disease
         iii. Obesity
         iv. Stress (Takotsubo)
v. Cardiotoxins
   (a) Alcohol
   (b) Cocaine
   (c) Chemotherapeutic agents
      (1) Anthracyclines
      (2) Cyclophosphamide (high dose)
      (3) Fluorouracil
      (4) Trastuzumab/pertuzumab
      (5) Mitoxantrone

vi. Myocarditis
vii. Idiopathic
viii. Tachycardia
ix. Peripartum

3. Heart failure with preserved EF (HFpEF) or diastolic dysfunction
   a. Defined as an LVEF of 50% or greater; borderline HFpEF is LVEF 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%).

4. Primary symptoms
   a. Dyspnea
   b. Fatigue
   c. Edema
   d. Exercise intolerance

5. Stages and functional class of HF according to the American College of Cardiology/American Heart Association (ACC/AHA) (Table 1)

<table>
<thead>
<tr>
<th>Stage</th>
<th>NYHA Functional Class</th>
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<tbody>
<tr>
<td>A</td>
<td>At high risk of HF (uncontrolled risk factors) but without structural heart disease or symptoms of HF</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but without signs or symptoms of HF</td>
</tr>
<tr>
<td></td>
<td>I  Asymptomatic HF; no limitations in physical activity caused by HF symptoms</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with prior or current symptoms of HF</td>
</tr>
<tr>
<td></td>
<td>I  No limitations in physical activity caused by HF symptoms</td>
</tr>
<tr>
<td></td>
<td>II Slight limitation of physical activity; asymptomatic at rest, but symptoms of HF with normal level of activity</td>
</tr>
<tr>
<td></td>
<td>III Marked limitations in physical activity because of HF symptoms; asymptomatic at rest</td>
</tr>
<tr>
<td></td>
<td>IV Symptoms of HF at rest or unable to carry out any physical activity</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions</td>
</tr>
<tr>
<td></td>
<td>IV Symptoms of HF at rest</td>
</tr>
</tbody>
</table>

HF = heart failure; NYHA = New York Heart Association.
6. Goals of therapy  
   a. Modify or control risk factors (e.g., HTN, obesity, DM)  
   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. HFpEF or systolic HF  
1. Pharmacologic therapy (Figure 1)  
   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: Inhibit reabsorption of Na in the ascending limb of the loop of Henle (loops) or in the distal tubule (thiazides)  
      vi. Dosing and administration considerations (Table 2)  
         (a) Should be combined with an angiotensin-converting enzyme (ACE) inhibitor, β-blocker, and aldosterone receptor antagonist (ARA)  
         (b) Start with a low initial dose and then double the dose and titrate according to the patient’s weight and diuresis as needed. Bioavailability differs between oral loop diuretics and must be considered when converting from one agent to another.  
         (c) If a patient has fluid overload, initiate and adjust therapy to result in 0.5-1 kg of weight loss per day (may be more aggressive in the inpatient setting).  
         (d) Long-term therapy should be adjusted to maintain a euvolemic state.  
         (e) A loop diuretic can be combined 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 magnesium as needed, especially with loop diuretics (goal with cardiovascular [CV] disease is K of 4.0 mEq/L or greater and magnesium of 2.0 mEq/L or greater to minimize the risk of arrhythmias). Monitor SCr and renal function to avoid acute kidney injury with overdiuresis.
Table 2. Diuretics and Recommended Dosing

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

\(^a\)Equivalent doses: furosemide 40 mg = bumetanide 1 mg = torsemide 10–20 mg = ethacrynic acid 50 mg.

\(^b\)Available in oral and intravenous formulations.

BID = twice daily.

b. ACE inhibitors
   i. Place in therapy: Recommended in all patients with HFrEF and current or prior symptoms, unless contraindicated (class I indication)
   ii. Benefits
      (a) Decreased mortality (about 25%–50% relative risk reduction compared with placebo depending on severity of HF)
      (b) Decreased hospitalizations (about 30% relative risk reduction compared with placebo)
      (c) Symptom improvement
      (d) Improved clinical status
      (e) Improved sense of well-being
      (f) Notable trials: CONSENSUS (enalapril), SOLVD (enalapril), SAVE (captopril), AIRE (ramipril), and TRACE (trandolapril).
   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 attenuate myocardial remodeling
iv. Dosing and administration considerations
(a) Start low and double the dose every 1–4 weeks to target dose (Table 3).
(b) ATLAS trial comparing patients with systolic dysfunction who received low-dose lisinopril (2.5–5 mg/day) and patients who received high-dose lisinopril (32.5–35 mg/day) showed no difference in all-cause mortality or CV mortality; however, the high-dose group did have a significant 12% lower risk of death or hospitalization for any reason and 24% fewer hospitalizations for HF.
(c) Patients may notice improvement in symptoms in several weeks.
(d) Avoid use in patients who have experienced angioedema as the result of previous ACE inhibitor use or those who are pregnant or plan to become pregnant.
(e) Use caution if SBP is less than 80 mm Hg, SCr is greater than 3 mg/dL, K is greater than 5.0 mEq/L, or the patient has bilateral renal artery stenosis.

v. Monitoring
(a) Monitor SCr and K for 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (preexisting hypotension, DM, K supplements, azotemia). SCr may rise (up to a 30% 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.
(b) Monitor BP and symptoms of hypotension (e.g., dizziness, lightheadedness).
   (1) BP may be low to begin with because of low CO.
   (2) BP = CO × Systemic vascular resistance (SVR).
   (3) In HF, as CO increases because of decreased SVR, BP may decrease slightly or remain the same.
   (4) Symptoms of hypotension are often not present with small dose increases. Remember to treat the patient, not the number.
(c) Ninety percent of people tolerate ACE inhibitors.
   (1) Angioedema (less than 1%): Can switch to angiotensin II receptor blockers (ARBs; cross-reactivity is 2.5%) or hydralazine–isosorbide dinitrate
   (2) Cough (20%): Can switch to ARBs (less than 1%)

Table 3. ACE Inhibitors and Recommended Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dosage</th>
<th>Target Dosage</th>
<th>Maximal Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg three times daily</td>
<td>50 mg three times daily</td>
<td>50 mg three times daily</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice daily</td>
<td>10 mg twice daily</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–5 mg daily</td>
<td>20 mg daily</td>
<td>40 mg daily</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg daily</td>
<td>8 mg daily</td>
<td>16 mg daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–2.5 mg daily</td>
<td>10 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg daily</td>
<td>4 mg daily</td>
<td>4 mg daily</td>
</tr>
</tbody>
</table>

Note: Fosinopril and quinapril can be used; however, they do not have the same magnitude of mortality-reducing data as listed above.

ACE = angiotensin-converting enzyme
c. Angiotensin receptor blockers
   i. Place in therapy
      (a) Recommended in patients with HFrEF with current or prior symptoms who are unable to take an ACE inhibitor (class I indication). Have not been proven superior to ACE inhibitors at target HF dosages.
      (b) 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)
      (c) Possibly considered if patient has experienced ACE inhibitor–induced angioedema (cross-reactivity 2.5%)
   ii. Benefits
      (a) Decreased HF-related hospitalizations and decreased death from CV causes.
      (b) Notable clinical trials: CHARM-Alternative (candesartan), VALIANT (valsartan), VAL-HEFT (valsartan), and HEAAL (losartan).
   iii. Mechanism of action
      (a) Selectively block the binding of angiotensin II to the angiotensin 1 receptor
      (b) Deters vasoconstriction and aldosterone-secreting effects
      (c) Does not affect ACE or inhibit kinin catabolism
   iv. Dosing and administration
      (a) Start low and double the dose every 1–4 weeks to target dose (Table 4).
      (b) Patients may notice improvement in symptoms in several weeks.
      (d) Avoid use in patients who have angioedema because of previous ARB use or those who are pregnant or plan to become pregnant.
      (e) Use caution if SBP is less than 80 mm Hg, Scr is greater than 3 mg/dL, K is greater than 5.0 mEq/L, or the patient has 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, DM, K supplements, azotemia)
         (1) Scr may rise (up to a 30% increase is acceptable) because of renal efferent artery dilation (results in a slightly decreased glomerular filtration rate).
         (2) Rarely, acute renal failure occurs, especially if the patient is intravascularly depleted (be careful to avoid overdiuresis).
      (b) Monitor BP and symptoms of hypotension (e.g., dizziness, lightheadedness).
      (c) Other adverse reactions
         (1) Angioedema (rare)
         (2) Cough (less than 1%)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dosage</th>
<th>Target Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>4–8 mg daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>25–50 mg daily</td>
<td>150 mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20–40 mg twice daily</td>
<td>160 mg twice daily</td>
</tr>
</tbody>
</table>

Table 4. ARBs and Recommended Dosing

*ARB = angiotensin receptor blocker.*
d. **β-blockers**

i. **Place in therapy**: Recommended in all patients with HFrEF with current or prior symptoms unless contraindicated (class I indication)

ii. **Benefits (when added to an ACE inhibitor)**
   - (a) Decreased mortality (about 35% relative risk reduction compared with placebo)
   - (b) Decreased hospitalizations (about 25% relative risk reduction compared with placebo)
   - (c) Symptom improvement
   - (d) Improved clinical status
   - (e) Notable clinical trials: CIBIS II (bisoprolol), MERIT-HF (metoprolol succinate), COPERNICUS (carvedilol), and COMET (metoprolol succinate vs. carvedilol).

iii. **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 α₁-blockade.
     1. Further decreases SVR (afterload)
     2. Results in greater reduction in BP than metoprolol succinate

iv. **Dosing and administration considerations**
   - (a) Only bisoprolol, carvedilol, and metoprolol succinate are recommended in HFrEF.
   - (b) Add to existing ACE inhibitor therapy (at least at a low dose) when HF symptoms are stable and patients are euvoletic.
   - (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) Might not notice improvement in symptoms for several months
   - (g) Should be considered even in patients with reactive airway disease or asymptomatic bradycardia

v. **Monitoring**
   - (a) BP, HR, and symptoms of hypotension or bradycardia (monitor in 1–2 weeks)
     1. Significant hypotension, bradycardia, or dizziness occurs in about 1% of patients 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) One percent to 2% more common than with placebo (in euvolemic, stable patients)
   (2) Responds to diuretic increase
(c) Fatigue or weakness
   (1) One percent 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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Starting Dosage</th>
<th>Target Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25 mg twice daily&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg daily</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>Metoprolol succinate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12.5–25 mg daily</td>
<td>200 mg daily</td>
</tr>
</tbody>
</table>

<sup>a</sup>50 mg twice daily if weight > 85 kg.
<sup>b</sup>Few or no data exist for metoprolol tartrate.
CR = controlled release

e. Aldosterone receptor antagonists
i. Place in therapy
   (a) Recommended in patients with NYHA class II–IV 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 myocardial infarction (MI) when they have an LVEF less than 40% with symptoms of HF or an LVEF less than 40% and DM (class I indication).

ii. Benefits of spironolactone in NYHA class III and IV HF (RALES trial)
   (a) Decreased mortality (30% relative risk reduction compared with placebo)
   (b) Decreased hospitalizations for HF (35% relative risk reduction compared with placebo)
   (c) Improved symptoms

iii. Benefits of eplerenone (selective ARA) in NYHA class II HF (EMPHASIS-HF)
   (a) Decreased composite endpoint of death from CV causes or hospitalization from HF (37% relative risk reduction compared with placebo)
   (b) Decreased death from CV causes (24% relative risk reduction compared with placebo)
   (c) Decreased hospitalizations for HF (42% relative risk reduction compared with placebo)
   (d) Decreased mortality (24% relative risk reduction compared with placebo)

iv. Benefits of eplerenone in left ventricular dysfunction after MI (EPHESUS)
   (a) Decreased mortality (15% relative risk reduction compared with placebo)
   (b) Decreased composite endpoint of death from CV causes or hospitalization for CV events (13% relative risk reduction compared with placebo)

v. Mechanism of action
   (a) Blocks effects of aldosterone in the kidneys, heart, and vasculature
   (b) Decreases K and magnesium loss; decreases ventricular arrhythmias
   (c) Decreases Na retention; decreases fluid retention
   (d) Eliminates catecholamine potentiation; decreases BP
   (e) 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 (or estimated glomerular filtration rate is greater than 30 mL/minute/1.73 m²), and K should be less than or equal to 5.0 mEq/L (Table 6).
   (c) In the absence of hypokalemia (K less than 4.0 mEq/L), supplemental K is not recommended when taking an ARA

Table 6. ARAs and Recommended Dosing

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Eplerenone</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated GFR ≥ 50 mL/min/1.73 m² and K ≤ 5 mEq/L</td>
<td>25 mg daily</td>
<td>12.5–25 mg daily</td>
</tr>
<tr>
<td>Maintenance dose after 1 mo if K ≤ 5 mEq/L and estimated GFR ≥ 50 mL/min/1.73 m²</td>
<td>50 mg daily</td>
<td>25 mg daily or twice daily</td>
</tr>
<tr>
<td>Estimated GFR 30–49 mL/min/1.73 m² and K ≤ 5 mEq/L</td>
<td>25 mg every other day</td>
<td>12.5 mg daily or every other day</td>
</tr>
<tr>
<td>Maintenance dose after 1 mo if K ≤ 5 mEq/L and estimated GFR 30–49 mL/min/1.73 m²</td>
<td>25 mg daily</td>
<td>12.5–25 mg daily</td>
</tr>
</tbody>
</table>

ARA = aldosterone receptor antagonist; GFR = glomerular filtration rate; K = potassium.

vii. Monitoring
   (a) K and Scr within 2–3 days, again at 7 days after starting therapy, monthly for first 3 months, and 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 trials; 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: Reported at a rate of 10% in clinical trials
      (2) Eplerenone can be considered as an alternative to spironolactone if gynecomastia is present.

f. Digoxin
   i. Place in therapy: Can be beneficial in decreasing hospitalizations in patients with HFrEF (class IIa indication); should be added after ACE inhibitor (or ARB) and β-blocker therapy
   ii. Benefits
       (a) Improved symptoms
       (b) Improved exercise tolerance
       (c) Decreased hospitalizations (28% relative risk reduction compared with placebo)
       (d) No effect on mortality
       (e) Notable clinical trial: DIG
   iii. Mechanism of action (in HF)
       (a) Inhibits myocardial Na-K adenosine triphosphatase
       (b) Decreases central sympathetic outflow by sensitizing cardiac baroreceptors
       (c) Decreases renal reabsorption of Na
       (d) Minimal increase in cardiac contractility
iv. Dosing and administration considerations
   (a) For most patients, 0.125 mg/day is adequate to achieve the desired serum concentration.
   (b) 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.
   (c) No indication to load patients with digoxin in the setting of HF
   (d) Avoid abrupt discontinuation; can precipitate clinical deterioration
   (e) Drug interactions: Digoxin concentrations are increased with concomitant:
      (1) Clarithromycin, erythromycin
      (2) Amiodarone (reduce digoxin dose by 30%–50% or reduce dosing frequency)
      (3) Dronedarone (reduce digoxin dose by 50%)
      (4) Itraconazole, posaconazole
      (5) Cyclosporine, tacrolimus
      (6) Verapamil

v. Monitoring
   (a) Serum concentrations should be less than 1 ng/mL; in general, concentrations of 0.5–0.9 ng/mL are suggested.
      (1) Minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations.
      (2) Risk of toxicity increases with age and renal impairment.
      (3) Risk of toxicity increases in the presence of hypokalemia, hypomagnesemia, or hypercalcemia.
      (4) Signs of toxicity generally include nausea, vomiting, vision changes.
   (b) SCr should be monitored because the drug is primarily cleared renally.

vi. 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 American with NYHA class III or IV HFpEF (class I indication)
   (b) May be useful in patients with current or prior symptoms of HFpEF who are unable to tolerate an ACE inhibitor or an ARB (class IIa indication)

ii. Benefits
   (a) Decreased mortality (43% relative risk reduction compared with placebo in African American patients)
   (b) Reduced pulmonary congestion and improved exercise tolerance
   (c) Notable clinical trials: V-HeFT and A-HeFT

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) Venous vasodilator (reduces preload)

iv. Dosing and administration considerations
   (a) Fixed-dose BiDil (hydralazine 37.5 mg plus isosorbide dinitrate 20 mg) with a goal dose of 2 tablets three times daily
   (b) Hydralazine 75 to 300 mg daily in 3 or 4 divided doses; isosorbide dinitrate 60–120 mg daily in 3 or 4 divided doses
v. Monitoring
   (a) Headache
   (b) Hypotension
   (c) Drug-induced lupus (with hydralazine)

h. Sacubitril/valsartan
   i. Place in therapy
      (a) Novel therapy approved by the U.S. Food and Drug Administration (FDA) in 2015
      (b) According to the 2017 ACC/AHA/Heart Failure Society of America focused update of the HF guidelines
         (1) The clinical strategy of inhibition of the renin-angiotensin-aldosterone system with ACE inhibitors (level of evidence: A) or ARBs (level of evidence: A), or sacubitril/valsartan (level of evidence: B) in conjunction with evidence-based β-blockers, and ARAs is recommended for patients with chronic HFrEF to reduce morbidity and mortality (class I recommendation)
         (2) In patients with chronic symptomatic NYHA class II or III HFrEF who can tolerate an ACE inhibitor or ARB, replacement by sacubitril/valsartan is recommended to further reduce morbidity and mortality (class I recommendation).
   ii. Benefits
      (a) Decreased composite endpoint of death from CV causes or hospitalization for HF (20% relative risk reduction compared with enalapril monotherapy)
      (b) Decreased all-cause mortality (16% relative risk reduction) and CV death (20% relative risk reduction) compared with enalapril monotherapy
      (c) Decreased hospitalization for HF (21% relative risk reduction compared with enalapril monotherapy)
      (d) Notable clinical trial: PARADIGM-HF
   iii. Mechanism of action
      (a) Sacubitril—prodrug metabolized to an active metabolite that inhibits neprilysin, increasing levels of natriuretic peptides
      (b) Valsartan—ARB, selectively blocks the angiotensin II receptor and inhibits angiotensin II–dependent aldosterone release
   iv. Dosing and administration considerations
      (a) Initial dose
         (1) Not currently taking ACE inhibitor or ARB, or switching from low doses of ACE inhibitor or ARB: sacubitril 24 mg/valsartan 26 mg twice daily
         (2) Switching from an ACE inhibitor or ARB at a standard dosage: sacubitril 49 mg/valsartan 51 mg twice daily
         (b) Maintenance dose: Double the dose every 2–4 weeks to a target dose of sacubitril 97 mg/valsartan 103 mg twice daily, as tolerated.
         (c) If switching from an ACE inhibitor, allow a 36-hour washout period before initiating sacubitril/valsartan.
   v. Monitoring
      (a) Observe for signs and symptoms of angioedema and hypotension.
      (b) Monitor renal function and K 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (e.g., preexisting hypotension, DM, K supplements, azotemia).
i. Ivabradine
   a. Place in therapy
   A Novel therapy approved by the FDA in 2015
   According to the 2017 ACC/AHA/Heart Failure Society of America focused update of the
   HF guidelines, ivabradine can be beneficial to reduce HF hospitalizations for patients with
   symptomatic (NYHA class II and III), stable, chronic HFrEF (LVEF of 35% or less) who
   are receiving evidence-based therapies, including a β-blocker at maximum tolerated dose,
   and who are in sinus rhythm (SR) with an HR of 70 beats/minute or greater at rest (class
   IIa recommendation).
   b. Benefits
   Decreased composite endpoint of CV death or hospitalization for HF (18% relative risk
   reduction compared with placebo)
   Decreased hospitalization for HF (26% relative risk reduction compared with placebo)
   Notable clinical trial: Systolic Heart Failure with the I Inhibitor Ivabradine Trial (SHIFT)
   c. Mechanism of action: Selectively inhibits the I current in the sinoatrial node, providing HR
   reduction
   d. Dosing and administration considerations
   Given the well-proven mortality benefits of β-blocker therapy, patients should be receiving
   β-blockers at maximally tolerated or target doses or have a contraindication to β-blocker
   therapy before assessing the resting HR for consideration of ivabradine initiation.
   Initial dosing: 5 mg twice daily
   After 2 weeks, adjust dose according to HR:
   Resting HR greater than 60 beats/minute: Increase dose by 2.5 mg twice daily.
   Resting HR 50–60 beats/minute: Continue current dose.
   Resting HR less than 50 beats/minute or signs/symptoms of bradycardia: Decrease
dose by 2.5 mg twice daily.
   Maximum dose: 7.5 mg twice daily
   e. Monitoring
   Assess HR and rhythm for bradycardia (6%–10%) and AF (5%–8%) after 2 weeks of
   therapy initiation or modification and periodically thereafter
   Phosphenes (3%): transient rings or spots of light in the visual field
j. Other medication therapies
i. Anticoagulation
   Recommended for HF with permanent, persistent, or paroxysmal AF with an additional
   risk factor for stroke (no preference on agent)
   Reasonable for patients with HF who have permanent, persistent, or paroxysmal AF with-
   out an additional risk factor for stroke
   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. Antiarrhythmics: Given the neutral effects on mortality, the preferred antiarrhythmics in
   patients with HFrEF are dofetilide (AF/atrial flutter) and amiodarone.
   Non-dihydropyridine (DHP) calcium channel blockers (CCBs) with negative inotropic effects
   can be harmful in patients with a low EF and should be avoided (class III recommendation: harm).
   DHP CCBs: DHP CCBs have no proven benefit on morbidity or mortality in HF. Use of
   amlodipine can be considered for HTN or ischemic heart disease management in HF patients
   because of its neutral effects on morbidity and mortality.
k. Device therapy
   i. Implantable cardioverter defibrillator recommended for primary prevention of sudden cardiac death in the following patients with ischemic or nonischemic HF/EF:
      (a) Patients with ischemic or nonischemic HF/EF (LVEF of 35% of less) and NYHA class II or III symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year, and patient must be at least 40 days post-MI (class I indication).
      (b) Patients with HF/EF (LVEF of 30% or less) resulting from previous MI and NYHA class I symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year, and patient should be at least 40 days post-MI (class I indication).
   ii. Chronic resynchronization therapy recommended for those with an LVEF of 35% or less, in SR, 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
   a. Prevent further cardiac injury.
      i. Discontinue smoking.
      ii. Reduce weight if obese.
      iii. Control HTN (goal BP < 130/80 mm Hg per the 2017 ACC/AHA/Heart Failure Society of America focused update of the HF guidelines)
      iv. Control DM.
   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
   d. Influenza and pneumococcal vaccines
   e. Monitor and appropriately replace electrolytes (to minimize risk of arrhythmias).
   f. Monitor for thyroid disease.
      i. Hypothyroidism can be masked by HF symptoms.
      ii. Hyperthyroidism will worsen systolic dysfunction.
   g. Screen for and treat depression.

**Patient Case**

3. Which drug that J.T. (from Patient Case 2) is currently taking would be best to discontinue because of his HF/EF?
   A. Acetaminophen.
   B. Sertraline.
   C. Cilostazol.
   D. Levothyroxine.
C. HFpEF or Diastolic Dysfunction: Clinical evidence for efficacious agents for HFpEF has generally been disappointing. Therapies for symptoms, comorbidities, and risk factors that can worsen CV disease are recommended.
   1. Class I recommendations
      a. SBP and diastolic blood pressure (DBP) should be well controlled. HTN impairs myocardial relaxation and promotes cardiac hypertrophy. Goal SBP less than 130 mm Hg per the 2017 ACC/AHA/Heart Failure Society of America focused update of the HF guidelines
      b. Diuretics should be used for symptom relief in volume overload.
   2. Class IIa recommendations
      a. Coronary revascularization is reasonable in patients with CHD who have angina or demonstrable myocardial ischemia that is judged to be symptomatic despite optimal therapy.
      b. Management of AF is reasonable to improve symptomatic HF.
      c. The use of β-blockers, ACE inhibitors, and ARBs in patients with HTN is reasonable to control BP.
3. Class IIb recommendation: Use of ARAs might be considered to decrease hospitalizations in HFrEF patients already on ACE inhibitors/ARBs and β-blockers.

4. Other recommendations
   a. 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 non-DHP CCBs
   b. Symptoms of breathlessness can be relieved using nitrates in addition to diuretics.

D. Medications Causing/Exacerbating HF: A recent Scientific Statement from the AHA addresses medications that can cause or exacerbate HF. Drugs to avoid or use with caution in HF include:

1. Nonsteroidal anti-inflammatory drugs (NSAIDs, including selective cyclooxygenase-2 inhibitors)
   a. Promote Na and water retention.
   b. Blunt diuretic response.
   c. Increase morbidity and mortality.

2. Corticosteroids: Promote Na and water retention.

3. Class I and III antiarrhythmic agents (except for amiodarone and dofetilide)
   a. Negative inotropic activity
   b. Proarrhythmic effects
   c. Amiodarone and dofetilide have been proved safe in patients with HF.
   d. Avoid dronedarone; it is contraindicated in patients with symptomatic HF with recent decompensa-
      tion necessitating hospitalization or NYHA class IV HF.

4. CCBs (except for amlodipine and felodipine)
   a. The use of negative inotropic activity is discouraged in the ACC/AHA guidelines.
   b. Promote neurohormonal activation.
   c. Amlodipine and felodipine have been proved safe in patients with HF and can be added when addi-
      tional BP reduction is needed; monitor for edema.

5. Minoxidil
   a. Promotes Na and water retention
   b. Stimulates the renin-angiotensin-aldosterone system

6. Thiazolidinediones: Promote Na and water retention

7. Metformin: Increased risk of lactic acidosis (black box warning)

8. Amphetamines (e.g., methylphenidate)
   a. α- and β-agonist activity
   b. Cause tachycardia
   c. Proarrhythmic effects

9. Cilostazol: Inhibits phosphodiesterase type 3

10. Itraconazole: Negative inotropic activity

11. Pregabalin
    a. Inhibits calcium channels
    b. Lower extremity edema, HF exacerbation

12. Nutritional supplements
    a. Lack of evidence
    b. Lack of regulation of products
    c. Potential for drug interactions and/or increased risk of bleeding

13. Hormonal therapies: may increase risk for adverse cardiovascular events
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. Potential symptoms that may be present to some degree include the following:
      i. Palpitations
      ii. Chest pain
      iii. Dyspnea
      iv. Fatigue
      v. Lightheadedness
   c. At worst, a thromboembolic event will occur or symptoms of HF may be present.
   d. Symptoms vary with ventricular rate, underlying LVEF, AF duration, and individual patient perceptions.

3. Classification
   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 SR using pharmacologic or nonpharmacologic options
   e. Nonvalvular: The absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

Patient Case

4. P.M. is a 52-year-old man (height 70 inches, weight 116 kg) 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 3-hour trip to his primary care provider. 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 HR of 74 beats/minute. A diagnosis of AF is made. What is the best approach for managing his AF at this time?
   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.
B. Pathophysiology
   1. Cardiac conduction (Figure 2)

   ![Diagram of Cardiac Conduction](image)

   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; ± 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.
   AV = atrioventricular; SA = sinoatrial.

   2. ECG findings

   ![ECG Image](image)

   **Figure 3.** Electrocardiogram showing atrial fibrillation.
3. AF causes (Table 7).

**Table 7. Potential Causes of Atrial Fibrillation**

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

C. Pharmacologic therapy

1. Ventricular rate control
   a. If patients have a rapid ventricular rate, AV nodal blockade is necessary.
   b. Goal HR (resting HR less than 80 beats/minute) is reasonable in symptomatic patients (class IIa recommendation). A more lenient rate control (resting HR less than 110 beats/minute) may be reasonable in patients who are asymptomatic and have LVEF preserved (class IIb recommendation).
   c. The 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.
      i. β-Blockers
         (a) Any agent with β-blockade can be used and dosed to the goal HR.
         (b) Labetalol or carvedilol if additional α₁-blockade is desirable (e.g., HTN)
         (c) Effective for controlling exercise-associated HR increases
         (d) Can be considered in patients with stable HFrEF (only carvedilol, metoprolol succinate, or bisoprolol)
         (e) Avoid in patients with Wolff-Parkinson-White syndrome.
      ii. Non-DHP 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 HFrEF
         (c) May be effective if additional HR control is needed when a patient is already 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, non-DHP CCBs, and digoxin
2. Rhythm control: Maintaining SR offers no advantage over controlling the ventricular rate (AFFIRM trial). 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**

<table>
<thead>
<tr>
<th>Rate control strategy</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Generally easy to achieve and maintain; out-of-hospital therapy typical</td>
<td>Electrical and structural remodeling because of continued AF makes future attainment of SR virtually impossible; safety not proven for younger patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rhythm control strategy</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If patient is symptomatic with fatigue and exercise intolerance, these symptoms may improve if SR is attained (especially in patients with HF); minimizes development of structural atrial changes; acceptable for all age groups</td>
<td>Adverse effects of antiarrhythmic medications; cost of medications and monitoring; likelihood of AF recurrence; in-hospital stay may be necessary to initiate therapy</td>
</tr>
</tbody>
</table>

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

**a. Cardioversion in AF**

i. If cardioversion is attempted (electric or pharmacologic), the absence of atrial thrombi must be ensured.

ii. Without anticoagulation (thrombi 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.

iii. Thrombi present plus cardioversion = 91% stroke rate.

iv. Ensure safe cardioversion by either:

   (a) Transesophageal echocardiogram (TEE) to visualize the atria, or
   (b) Three or more weeks of therapeutic anticoagulation (INR greater than 2.0 if warfarin is selected) (Table 9)
Table 9. Anticoagulation Strategies Surrounding Cardioversion of AFa

<table>
<thead>
<tr>
<th>AF Type</th>
<th>Anticoagulation Recommendations</th>
</tr>
</thead>
</table>
| Unstable AF                   | • Synchronized cardioversion; anticoagulate immediately beforehand  
• Anticoagulate for ≥4 wk after cardioversion if AF ≥ 48 hr or if duration is unknown  
ACC/AHA/HRS AF guidelines  
• Need for anticoagulation before, according to stroke risk  
• High risk: UFH, LMWH, or DOAC as soon as possible  
• Need for anticoagulation after cardioversion should be based on the patient’s risk of thromboembolism, according to their CHA2DS2-VASc score  
ACC/AHA/HRS AF guidelines  
• Anticoagulate for 3 wk before cardioversion  
• Warfarin with INR 2.0–3.0, LMWH at full treatment dose, or dabigatran  
• Anticoagulate for ≥4 wk after cardioversion, regardless of baseline risk of stroke  
ACC/AHA/HRS AF guidelines  
• Anticoagulate for 4 wk after cardioversion, regardless of CHA2DS2-VASc score  
ACC/AHA/HRS AF guidelines  
• If no identifiable thrombus seen on TEE, cardioversion is reasonable, provided anticoagulation is achieved before TEE  
• Anticoagulation should be maintained after cardioversion for ≥4 wk  |
| Stable AF, duration <48 hr (no TEE) | ACCP (CHEST) guidelines:  
• Anticoagulate for 3 wk before cardioversion  
• Warfarin with INR 2.0–3.0, LMWH at full treatment dose, or dabigatran  
• Anticoagulate for ≥4 wk after cardioversion, regardless of baseline risk of stroke  
ACC/AHA/HRS AF guidelines  
• Anticoagulate for 4 wk after cardioversion, regardless of CHA2DS2-VASc score  
ACC/AHA/HRS AF guidelines  
• If no identifiable thrombus seen on TEE, cardioversion is reasonable, provided anticoagulation is achieved before TEE  
• Anticoagulation should be maintained after cardioversion for ≥4 wk  |
| Stable AF, duration unknown or ≥48 hr (with TEE-guided cardioversion) | ACCP (CHEST) guidelines:  
• TEE-guided therapy with abbreviated anticoagulation before cardioversion  
• LMWH or UFH at full treatment doses should be initiated at the time of TEE, and cardioversion should be performed within 24 hr of TEE if no thrombus is seen  
• Anticoagulate for ≥4 wk after cardioversion, regardless of baseline risk of stroke  
ACC/AHA/HRS AF guidelines  
• If no identifiable thrombus seen on TEE, cardioversion is reasonable, provided anticoagulation is achieved before TEE  
• Anticoagulation should be maintained after cardioversion for ≥4 wk  |

aPotential risk of cardioversion with antiarrhythmic drugs should be considered before treatment initiation.

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

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

c. Oral antiarrhythmic agents to induce or maintain SR (choice of agent depends on patient comorbidities)
   i. Class Ic antiarrhythmics: 50% efficacy
      (a) Flecainide and propafenone can be considered first-line therapies for patients without structural heart disease (Figure 4). Propafenone also displays some independent non-selective β-blocking properties.
      (b) Concomitant AV nodal blocking agent (β-blocker or non-DHP CCB) typically required
      (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 (e.g., 400 mg 2 or 3 times per day for 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, which may help to control HR if AF recurs
         (5) May use in patients with HF
         (6) Hepatically metabolized: Cytochrome P450 (CYP) 3A4 substrate; inhibitor of CYP3A4, CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein (P-gp)
         (7) Minimal incidence of ventricular arrhythmias
         (8) Drug interactions (many)
            (A) Digoxin: Increased digoxin exposure. Lower digoxin dose by 50%.
            (B) Warfarin: Increased warfarin exposure. Lower warfarin dose by 33%–50%.
            (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, non-DHP CCBs, clonidine, ivabradine: 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) ECG: Periodically
            (E) Pulmonary function tests (including DL CO [carbon dioxide diffusion in the lungs]): Baseline and for unexplained cough/dyspnea, chest radiographic abnormalities or clinical suspicion. Discontinue if pulmonary fibrosis occurs.
            (F) Ophthalmologic examination: Baseline (if visual impairment) and periodically or for symptoms of visual impairment. Discontinue if optic neuritis occurs.
            (G) Skin toxicities: “Blue skin” syndrome and sunburn
            (H) Neurologic toxicity: Tremor, neuropathy
            (I) Gastrointestinal (GI) adverse effects
      (b) Sotalol: 50%–60% efficacy
         (1) Renal excretion. Dose adjustment and vigilant corrected QT (QTc) interval monitoring necessary in renal impairment. Recommended starting dose is 80 mg twice daily (unless creatinine clearance [CrCl] less than 60 mL/minute, then once daily).
         (2) Should be initiated in the hospital (minimum of 3-day stay), where QTc interval, serum electrolytes (e.g., K and magnesium), and renal function can be monitored
         (3) Contraindicated in patients with uncontrolled HF; CrCl less than 40 mL/minute; QTc interval greater than 450 milliseconds; and second- or third-degree AV block or sick sinus syndrome (in absence of pacemaker)
Possesses nonselective β-blocking properties; may result in additive bradycardia with β-blockers, non-DHP CCBs, clonidine, ivabradine, and digoxin

Dofetilide: 50%–60% efficacy

Should be initiated in the hospital (minimum of 3-day stay) so that QTc interval, serum electrolytes (e.g., K and magnesium), and renal function can be monitored

Starting dose is selected based on renal function

- CrCl 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

Modification of subsequent doses is based on QTc interval measured 2–3 hours after initial dose: QTc > 500 milliseconds (or 550 milliseconds in ventricular conduction abnormalities) OR QTc increased greater than 15% above baseline: reduce dose by 50%

If QTc is greater than 500 milliseconds (or 550 milliseconds in ventricular conduction abnormalities) at any point after in-hospital doses 2–5, discontinue dofetilide

Hepatically metabolized by CYP3A4

Renal elimination through renal cationic secretion; check QTc interval if renal function declines

Contraindicated in patients with CrCl less than 20 mL/minute or QTc interval greater than 440 milliseconds (or 500 milliseconds for patients with ventricular conduction abnormalities)

May use in patients with HF

Drug interactions

- Avoid concomitant use of the following drugs: cimetidine, verapamil, itraconazole, ketoconazole, hydrochlorothiazide, prochlorperazine, megestrol, dolutegravir, and trimethoprim alone or in combination with sulfamethoxazole
- Use CYP3A4 inhibitors, triamterene, metformin, and amiloride with caution: increased dofetilide exposure

Dronedarone: 21%–25% efficacy

- Amiodarone analog lacking the iodine moiety that contributes to the thyroid toxicity of amiodarone
- Has electrophysiologic properties of classes I–IV
- Dose: 400 mg twice daily with morning and evening meal
- Hepatically metabolized; CYP3A4 substrate; CYP3A4, CYP2D6, and P-gp inhibitor
- Half-life is 13–19 hours.
- Small increase in SCr by 0.1 mg/dL probably a result of inhibition of creatinine’s tubular secretion; rapid onset, will plateau after 7 days, and is reversible. Monitor SCr periodically.
- Acute kidney injury has also been reported, and it is usually reversible with drug discontinuation.
- Contraindicated in permanent AF; NYHA class II or III HF with recent decompensation necessitating hospitalization; NYHA class IV HF; second- or third-degree AV block or sick sinus syndrome (in absence of pacemaker); 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 500 milliseconds or greater
- One meta-analysis found dronedarone less effective than amiodarone for the maintenance of SR, but with fewer adverse effects.
(10) Drug interactions

- **Digoxin**: Increased digoxin exposure; lower digoxin dose by 50%
- **B-Blockers, non-DHP CCBs, and clonidine**: Excessive bradycardia; initiate these drugs at lowest dose. Diltiazem and verapamil can increase dronedarone exposure; therefore, monitor ECG.
- **Statins**: Increased statin exposure. Limit dose of simvastatin to 10 mg/day and lovastatin to 20 mg/day.
- **Dabigatran**: In patients with moderate renal impairment (CrCl 30–50 mL/minute), dronedarone increases dabigatran exposure; decrease dabigatran dose to 75 mg twice daily.
- **Strong CYP3A4 inhibitors and inducers**: Avoid.
- **Cyclosporine, tacrolimus, sirolimus**: Increased exposure of these agents; monitor serum concentrations closely

(11) Other safety issues

- **Liver injury**: According to postmarketing surveillance, dronedarone has been associated with rare but severe hepatic liver injury.
- **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).

**Figure 4.** Options for rhythm control in patients with paroxysmal and persistent atrial fibrillation. Antiarrhythmics are listed in alphabetical order and not order of preference

*Depends on patient preference when performed in experienced centers.
*Not recommended with severe left ventricular hypertrophy (wall thickness > 1.5 cm).
*Use with caution in patients at risk of torsades de pointes ventricular tachycardia.
*Should be combined with atrioventricular nodal blocking agents.
*Catheter ablation is only recommended as first-line therapy for patients with paroxysmal atrial fibrillation (class IIa recommendation).
CHD = coronary heart disease; HF = heart failure.

4. Antithrombotic therapy
   a. The average annual stroke rate is 5% per year without anticoagulation.
      i. A patient’s individual risk can vary from about 1% to 20% per year depending on risk factors.
      ii. This risk is independent of current cardiac status (i.e., SR or AF).
   b. Risk stratification and treatment determination is based on the CHA₂DS₂-VASc score (Tables 10–11)

Table 10. Risk Stratification for Antithrombotic Therapy Using the CHA₂DS₂-VASc Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF or LVEF ≤ 40%</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 yr</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke, TIA, thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 yr</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
</tr>
</tbody>
</table>

*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. Recommendations for Antithrombotic Therapy Based on CHA₂DS₂-VASc Score

<table>
<thead>
<tr>
<th>CHA₂DS₂-VASc Score</th>
<th>Reasonable to omit antithrombotic therapy</th>
<th>CHA₂DS₂-VASc Score</th>
<th>No antithrombotic therapy or treatment with an OAC or aspirin may be considered</th>
<th>OAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>= 0</td>
<td>Reasonable to omit antithrombotic therapy</td>
<td>= 1</td>
<td>CHA₂DS₂-VASc Score = 2</td>
<td>CHA₂DS₂-VASc Score ≥ 2</td>
</tr>
</tbody>
</table>

OAC = oral anticoagulant.

Table 12. Comparison of the Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Factor II (thrombin) inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td>Impact on coagulation assay</td>
<td>aPTT (~2×) ↑ INR ↑</td>
<td>aPTT 40% ↑ INR ↑</td>
<td>↑ aPTT, PT, and INR</td>
<td>↑ aPTT, PT, and INR</td>
</tr>
<tr>
<td>Peak</td>
<td>1–3 hr</td>
<td>2–4 hr</td>
<td>3–4 hr</td>
<td>1–2 hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>12–17 hr</td>
<td>5–13 hr</td>
<td>8–15 hr</td>
<td>10–14 hr</td>
</tr>
<tr>
<td>Percentage undergoing renal elimination</td>
<td>80%</td>
<td>36%</td>
<td>27%</td>
<td>~50%</td>
</tr>
<tr>
<td>Dialyzable</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CYP metabolism</td>
<td>No</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>No</td>
</tr>
<tr>
<td>P-glycoprotein substrate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

aPTT = activated partial thromboplastin time; CYP = cytochrome P450; INR = international normalized ratio; PT = prothrombin time.
### Table 13. Major Outcomes of Direct Oral Anticoagulants versus Adjusted-Dose Warfarin in Atrial Fibrillation Trials

<table>
<thead>
<tr>
<th>Outcome (RR ± 95% CI)</th>
<th>RE-LY (Dabigatran 150 mg BID)</th>
<th>ROCKET-AF (Rivaroxaban 20 mg/day)</th>
<th>ARISTOTLE (Apixaban 5 mg BID)</th>
<th>ENGAGE-AF (Edoxaban 60 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS₂ score</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Warfarin TTR</td>
<td>64%</td>
<td>55%</td>
<td>62.2%</td>
<td>68.4%</td>
</tr>
<tr>
<td>Stroke/SEE</td>
<td>0.66 (0.53–0.82)</td>
<td>0.88 (0.75–1.03)</td>
<td>0.79 (0.66–0.95)</td>
<td>0.79 (0.63–0.99)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.76 (0.59–0.97)</td>
<td>0.94 (0.75–1.17)</td>
<td>0.92 (0.74–1.13)</td>
<td>1.00 (0.83–1.19)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.26 (0.14–0.49)</td>
<td>0.59 (0.37–0.93)</td>
<td>0.51 (0.35–0.75)</td>
<td>0.54 (0.38–0.77)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.93 (0.81–1.07)</td>
<td>1.04 (0.90–1.20)</td>
<td>0.69 (0.60–0.80)</td>
<td>0.80 (0.71–0.91)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.40 (0.27–0.60)</td>
<td>0.67 (0.47–0.93)</td>
<td>0.42 (0.30–0.58)</td>
<td>0.47 (0.34–0.63)</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.85 (0.72–0.99)</td>
<td>0.89 (0.73–1.10)</td>
<td>0.89 (0.76–1.04)</td>
<td>0.86 (0.77–0.97)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.88 (0.77–1.00)</td>
<td>0.85 (0.70–1.02)</td>
<td>0.89 (0.80–0.998)</td>
<td>0.92 (0.83–1.01)</td>
</tr>
</tbody>
</table>

*Patients with a CrCl < 30 mL/min were excluded from RE-LY, ROCKET-AF, and ENGAGE-AF trials; patients with a CrCl < 25 mL/min were excluded from ARISTOTLE trial. Patients with mechanical heart valves were excluded from all trials. Patients with bioprosthetic valves were excluded from RE-LY, ROCKET-AF, and ARISTOTLE trials.  
*Dose adjusted to 15 mg daily for CrCl 30–49 mL/min.  
*Dose adjusted to 2.5 mg BID for two or more of the following: age ≥ 80 yr, SCr ≥ 1.5 mg/dL, body weight < 60 kg.  
*Dose adjusted to 30 mg daily if CrCl 30–50 mL/min, body weight ≤ 60 kg, or concomitant use of verapamil, quinidine, or dronedarone; concomitant use of azithromycin, clarithromycin, ketoconazole, itraconazole, cyclosporine, and ritonavir was prohibited.  
BID = twice daily; CI = confidence interval; CrCl = creatinine clearance; CV = cardiovascular; RR = relative risk; SCr = serum creatinine; SEE = systemic embolic event; TTR = time in therapeutic international normalized ratio range.

c. Dabigatran (Tables 12 and 13)  
   i. Direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF; demonstrated superiority to warfarin for efficacy  
   ii. Dose:  
      (a) CrCl greater than 30 mL/minute: 150 mg twice daily  
      (b) CrCl 15–30 mL/minute: 75 mg twice daily  
      (c) CrCl less than 15 mL/minute: No dosing recommendations available  
      (d) Swallow capsules whole (do not break, crush, or chew).  
   iii. Antidote: Idarucizumab  
      (a) Indicated for emergency surgery or urgent procedures or in life-threatening or uncontrolled bleeding.  
      (b) Dosing: Administer 5 g (as 2 separate 2.5-g doses no more than 15 minutes apart) intravenously. May consider a second dose if coagulation parameters re-elevate, clinically relevant bleeding occurs, or a second emergency surgery/urgent procedure is indicated  
   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 (Box 1)

Box 1. Dabigatran Conversion Strategies to and from Oral and Parenteral Anticoagulants

<table>
<thead>
<tr>
<th>Converting from dabigatran to warfarin</th>
<th>CrCl &gt; 50 mL/min</th>
<th>Start warfarin 3 days before discontinuing dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl 31–50 mL/min</td>
<td>Start warfarin 2 days before discontinuing dabigatran</td>
<td></td>
</tr>
<tr>
<td>CrCl 15–30 mL/min</td>
<td>Start warfarin 1 day before discontinuing dabigatran</td>
<td></td>
</tr>
<tr>
<td>CrCl &lt; 15 mL/min</td>
<td>No dosing recommendations are available</td>
<td></td>
</tr>
</tbody>
</table>

**Converting from dabigatran to parenteral anticoagulants**

For patients currently taking dabigatran, wait 12 hr (CrCl > 30 mL/min) or 24 hr (CrCl < 30 mL/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant

**Converting from parenteral anticoagulants to dabigatran**

Start dabigatran 0–2 hr before the next dose of the parenteral drug was to have been administered (e.g., LMWH) or when a continuously administered parenteral drug is discontinued (e.g., intravenous UFH)

**Converting from warfarin to dabigatran**

Discontinue warfarin and start dabigatran when the INR < 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 ≥2 days.

CrCl = creatinine clearance; INR = international normalized ratio; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

vi. Drug interactions: Dabigatran is a substrate of P-gp.
   (a) P-gp inducers (e.g., only rifampin mentioned in package labeling) should be avoided.
   When using dabigatran in combination with dronedarone and ketoconazole (P-gp inhibitors) in patients with moderate renal impairment (CrCl 30–50 mL/minute), reduce the dabigatran dose to 75 mg twice daily.
   (b) Dabigatran should not be used in combination with P-gp inhibitors in the setting of severe renal impairment (CrCl less than 30 mL/minute).

IV. Rivaroxaban (Tables 12 and 13)
   i. Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF; demonstrated noninferiority compared with warfarin for efficacy
   ii. Dose
      (a) CrCl greater than 50 mL/minute: 20 mg/day with evening meal
      (b) CrCl 15–50 mL/minute: 15 mg/day with evening meal
      (c) CrCl less than 15 mL/minute: Avoid use
      (d) Can be administered by nasogastric tube or gastric feeding tube (crush tablets and suspend in 50 mL of water). Tablets can also be crushed and mixed in applesauce.
   iv. Antidote: None approved by the FDA to date (in the pipeline)
v. Converting from or to warfarin or other anticoagulants (Box 2)

**Box 2. Rivaroxaban Conversion Strategies to and from Oral and Parenteral Anticoagulants**

<table>
<thead>
<tr>
<th>Converting from rivaroxaban to warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken. Discontinue the parenteral anticoagulant when the INR reaches an acceptable range.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Converting from rivaroxaban to anticoagulants (with rapid onset) other than warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue rivaroxaban, and give the first dose of the other anticoagulant (oral or parenteral; other than warfarin) at the time that the next rivaroxaban dose would have been taken.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Converting from warfarin to rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue warfarin and initiate rivaroxaban once INR &lt; 3.0.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Converting from anticoagulants (with rapid onset) other than warfarin to rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begin rivaroxaban 0–2 hours before the next scheduled evening administration of the drug (e.g., LMWH or non-warfarin oral anticoagulant), and do not administer the other anticoagulant. For UFH administered by continuous infusion, stop the infusion and start rivaroxaban at the same time.</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; LMWH = low-molecular weight heparin; UFH = unfractionated heparin.

vi. Drug interactions. Rivaroxaban is a substrate of CYP3A4/5 and P-gp.

   (a) Combined strong dual inhibitors of CYP3A4 and P-gp (ketoconazole, ritonavir): Avoid administration of rivaroxaban.

   (b) Combined strong dual inducers of CYP3A4 and P-gp (carbamazepine, phenytoin, rifampin, St. John’s wort): Avoid administration of rivaroxaban.

   (c) Combined P-gp inhibitors and moderate CYP3A4 inhibitors (erythromycin) in the setting of renal impairment (CrCl 15–<80 mL/minute): Avoid administration of rivaroxaban.

e. Apixaban (Tables 12 and 13)

   i. Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF; demonstrated superiority over warfarin for efficacy

   ii. Dose

      (a) 5 mg twice daily unless:

         (1) In patients with at least two of the following characteristics (age 80 years or older, body weight of 60 kg or less, or SCr of 1.5 mg/dL or greater) the recommended dose is 2.5 mg twice daily.

         (2) CrCl less than 15 mL/minute, no specific recommendations

         (3) End-stage renal disease maintained on hemodialysis, 5 mg twice daily. In patients with end-stage renal disease maintained with hemodialysis who are 80 years and older and/or weigh 60 kg or less, 2.5 mg twice daily

      (b) Can be crushed and suspended in water, dextrose 5% in water, apple juice, or apple sauce and administered orally

      (c) Can be administered by nasogastric tube (crush tablets and suspend in 60 mL water or dextrose 5% in water and administer immediately)

iii. Antidote: None approved by the FDA to date (in the pipeline)
iv. Converting from or to warfarin or other anticoagulants (Box 3)

**Box 3. Apixaban Conversion Strategies to and from Oral and Parenteral Anticoagulants**

**Converting from apixaban to warfarin**
Discontinue apixaban, and begin both a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken. Discontinue the parenteral anticoagulant when the INR reaches an acceptable range.

**Converting from apixaban to anticoagulants (with rapid onset) other than warfarin**
Discontinue apixaban, and begin the new anticoagulant (oral or parenteral; other than warfarin) at the usual time of the next dose of apixaban.

**Converting from warfarin to apixaban**
Warfarin should be discontinued and apixaban initiated when INR < 2.0.

**Converting from anticoagulants (with rapid onset) other than warfarin to apixaban**
Discontinue the anticoagulant (oral or parenteral; other than warfarin), and begin taking apixaban at the usual time of the next dose of the other anticoagulant.

INR = international normalized ratio

v. Drug interactions: Apixaban is a substrate of CYP3A4 and P-gp.
   (a) Combined strong dual CYP3A4 and P-gp 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-gp (rifampin, carbamazepine, phenytoin, or St. John’s wort): Avoid concomitant use.

f. Edoxaban (Tables 12 and 13)
   i. Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF; demonstrated noninferiority compared with warfarin for efficacy
   ii. Dose
      (a) Dosage is 60 mg once daily in patients with CrCl of 51 mL/minute to 95 mL/minute
      (b) CrCl greater than 95 ml/minute: Avoid use.
      (c) CrCl 15–50 mL/minute: Reduce dose to 30 mg once daily.
      (d) CrCl less than 15 mL/min: Avoid use.
      (e) There are no data on administering edoxaban by feeding tubes or with crushing the medication to mix with other foods or liquids.
   iii. Antidote: None approved by the FDA to date (in the pipeline)
iv. Converting from or to warfarin or other anticoagulants (Box 4)

Box 4. Edoxaban Conversion Strategies to and from Oral and Parenteral Anticoagulants

<table>
<thead>
<tr>
<th>Converting from edoxaban to warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral option: For patients taking 60 mg of edoxaban, reduce the dose to 30 mg and begin warfarin concomitantly. For patients receiving 30 mg of edoxaban, reduce the dose to 15 mg and begin warfarin concomitantly. The INR must be measured at least weekly and just before the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR ≥ 2.0 is achieved, edoxaban should be discontinued and warfarin continued.</td>
</tr>
<tr>
<td>Parenteral option: Discontinue edoxaban, and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR ≥ 2.0 is achieved, the parenteral anticoagulant should be discontinued and warfarin continued.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Converting from edoxaban to anticoagulants (with rapid onset) other than warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue edoxaban, and begin the new anticoagulant (oral or parenteral; other than warfarin) at the usual time of the next dose of edoxaban.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Converting from warfarin to edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue warfarin and start edoxaban when the INR ≤ 2.5.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Converting from anticoagulants (with rapid onset) other than warfarin to edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue the other oral anticoagulant (other than warfarin) or LMWH, and begin taking edoxaban at the usual time of the next dose of the other anticoagulant. For UFH administered by continuous infusion, stop the infusion and start edoxaban 4 hours later.</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; LMWH = low-molecular weight heparin; UFH = unfractionated heparin.

v. Drug interactions: Edoxaban undergoes minimal metabolism by hydrolysis, conjugation, and oxidation by CYP3A4. Edoxaban is a P-gp substrate; avoid use with P-gp inducers (e.g., only rifampin mentioned in package labeling).

g. Warfarin

i. Inhibits vitamin K–dependent clotting factors II, VII, IX, 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 AF. 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, HF, 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. It 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, hold one or two doses and resume at a lower dose.
(d) If INR was previously stable or therapeutic and single out-of-range INR is 0.5 or less above or below therapeutic range, the current dose can be continued; 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, and valvular AF or for those who are stable on warfarin or are not otherwise candidates for direct oral anticoagulant therapy

v. Antidote: Vitamin K

vi. Drug interactions
(a) Reduced warfarin absorption (e.g., cholestyramine, sucralfate)
(b) Enzyme induction (decreases INR and warfarin effects): CYP3A4 inducers (e.g., rifampin, carbamazepine, phenobarbital, St. John’s wort)
(c) Enzyme inhibition (increases INR and warfarin effects)
(1) S-warfarin (CYP2C9 inhibitors) (e.g., metronidazole, trimethoprim/sulfamethoxazole, fluconazole, isoniazid, fluoxetine, sertraline, amiodarone, clopidogrel)
(2) R-warfarin (CYP3A3/4/5 inhibitors; e.g., clarithromycin, erythromycin, “azole” antifungals, nefazodone, fluoxetine, amiodarone, cyclosporine, sertraline, grapefruit juice, ciprofloxacin, protease inhibitors, diltiazem, verapamil, isoniazid, metronidazole)
(d) Drugs with antiplatelet effects (e.g., gingko, garlic, aspirin, NSAIDs, clopidogrel, ticagrelor, prasugrel, 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)
(g) Drugs that reduce vitamin K synthesis in the intestinal flora (e.g., antibiotics)

vii. 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 reveals an LVEF of 35%–40%. H.D.’s physician would like to continue a rhythm control approach. What is the best treatment option 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 (procedures)
1. Electrical cardioversion (low-energy cardioversion; sedation highly desirable; can be used for elective cardioversion or in emergent cardioversion 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: HTN is a persistent, nonphysiologic elevation of BP; it is defined as (1) having an SBP of 140 mm Hg or greater; (2) having a DBP of 90 mm Hg or greater; (3) taking antihypertensive medication; or (4) having been told at least twice by a physician or other health professional that one has HTN.

A. Background
1. Prevalence
   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. Obesity is a contributor
      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 treating elevated BP
   a. Decreased risk of stroke (by 35-40%)
   b. Decreased risk of MI (by 20-25%)
   c. Decreased risk of HF (by 50%)
5. Effects of lifestyle modifications on BP (Table 14)

Table 14. Recommended Lifestyle Modifications

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain a normal body weight (BMI 18.5–24.9 kg/m²)</td>
<td>5–20 mm Hg per 10-kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan (includes substantial K intake)</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat</td>
<td>8–14 mm Hg</td>
</tr>
<tr>
<td>Reduce Na intake</td>
<td>Reduce Na intake to ≤ 2400 mg/day</td>
<td>2–8 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Reducing Na intake further to ≤ 1500 mg/day is associated with greater BP reduction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reducing Na intake by at least 1000 mg/day will lower BP if desired daily Na intake goal is not achieved</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day most days of the week)</td>
<td>4–9 mm Hg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to: Men: 2 drinks/day (24 oz of beer, 10 oz of wine, or 3 oz of 80-proof whiskey)</td>
<td>2–4 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Women and those of lower body weight: 1 drink/day</td>
<td></td>
</tr>
</tbody>
</table>

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

B. Therapeutic management

1. Patient classification and management in adults: Primary classification based on SBP (Table 15)

Table 15. Classification of BP and Hypertension and Lifestyle Modification Recommendations

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>Lifestyle Modifications or Pharmacologic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP goal*</td>
<td>&lt; 140</td>
<td>and</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140–159</td>
<td>or</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥ 160</td>
<td>or</td>
<td>≥ 100</td>
</tr>
</tbody>
</table>

*This is the BP goal for most patients. Lower or higher targets may be needed in certain patient populations. See Table 16.

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

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 CKD or DM and black patients.
   b. Several guidelines address BP goals for specific disease states. These goals are outlined in Table 16.

---

**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, and the medication was continued upon discharge. An echocardiogram before discharge showed an LVEF greater than 60%. His vital signs include BP 150/94 mm Hg and HR 80 beats/minute. His laboratory results include Na 139 mEq/L, K 4.4 mEq/L, and SCr 1.2 mg/dL. What 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 DM treated with glyburide 5 mg/day. She presents to the clinic for a routine follow-up of her DM. 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, blood urea nitrogen 14 mg/dL, SCr 1.0 mg/dL, and 24-hour urine albumin 36 mg/24 hours. At her last visit, her BP was 136/85 mm Hg. What is the best approach for managing her HTN?
   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.
### Table 16. Goal BP Values Recommended by Various Organizations (goals vary)

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Goal BP (mm Hg)</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population ≥ 60 yr</td>
<td>&lt; 150/90</td>
<td>JNC8, ACP/AAFP</td>
</tr>
<tr>
<td>General population &lt; 60 yr</td>
<td>&lt; 140/90</td>
<td>JNC8</td>
</tr>
<tr>
<td>Adults 18–80 yr</td>
<td>&lt; 140/90</td>
<td>ASH/ISH</td>
</tr>
<tr>
<td>Patients with DM ≥ 18 yr (a lower SBP target of &lt; 130 mm Hg may be appropriate in patients at high risk of cardiovascular disease if can be achieved without undue treatment burden)</td>
<td>&lt; 140/90</td>
<td>ADA</td>
</tr>
<tr>
<td>Pregnancy with DM</td>
<td>120-160/80-105</td>
<td>ADA</td>
</tr>
<tr>
<td>Patients with CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In adults both with and without DM having a urine albumin excretion &lt; 30 mg/24 hr (or equivalent) whose BP is consistently &gt; 140/90 mm Hg</td>
<td>≤ 140/90</td>
<td>JNC8, KDIGO KDIGO</td>
</tr>
<tr>
<td>In adults both with and without DM having a urine albumin excretion ≥ 30 mg/24 hr (or equivalent) whose BP is consistently &gt; 130/80 mm Hg</td>
<td>≤ 130/80</td>
<td>ADA, KDIGO</td>
</tr>
<tr>
<td>Patients with HFpEF or HFpEF</td>
<td>SBP &lt; 130</td>
<td>ACC/AHA/HFSA</td>
</tr>
<tr>
<td>Patients with stage A HF</td>
<td>&lt;130/80</td>
<td>ACC/AHA/HFSA</td>
</tr>
<tr>
<td>Patients with CHD</td>
<td>&lt; 140/90</td>
<td>AHA/ACC/ASH</td>
</tr>
<tr>
<td>Patients ≥ 60 yr with a history of stroke or transient ischemic attack (TIA)</td>
<td>SBP &lt; 140</td>
<td>ACP/AAFP</td>
</tr>
<tr>
<td>SBP ≤ 140 SBP 140–145 (Avoid SBP &lt; 130 and DBP &lt; 65)</td>
<td>SBP &lt; 140</td>
<td>ACCF/AHA</td>
</tr>
<tr>
<td>Older adult patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 55–79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exceptions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) In patients for whom an SBP &lt; 150 mm Hg is readily and safely obtained with just one or two drugs, further intensification of treatment to achieve a value &lt; 140 mm Hg may be considered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(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 (&lt; 65 mm Hg)</td>
<td>SBP ≤ 140 SBP 140–145 (Avoid SBP &lt;130 and DBP &lt; 65)</td>
<td>ACCF/AHA ACCF/AHA</td>
</tr>
</tbody>
</table>

1High cardiovascular risk is defined as known vascular disease, diabetes, older patients with CKD and eGFR <45 mL/min/1.73m², metabolic syndrome, and older patients

2Weak recommendation; guidelines recommend selecting treatment goals based on periodic discussion of benefits and harms of blood pressure targets

ACCF/AHA = American College of Cardiology/American Heart Association/Heart Failure Society of America; AHA/AAFP = American College of Physicians/American Academy of Family Physicians; ADA = American Diabetes Association; AHA/ACC/ASH = American Heart Association/American Society of Hypertension; ASH/ISH = American Society of Hypertension/International Society of Hypertension; BP = blood pressure; CHD = coronary heart disease; CKD = chronic kidney disease; DBP = diastolic blood pressure; DM = diabetes mellitus; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; JNC = Joint National Committee; KDIGO = Kidney Disease: Improving Global outcomes; SBP = systolic blood pressure.


3. HTN treatment algorithm

**Stage 1 hypertension**
SBP 140–159 mm Hg or DBP 90–99 mm Hg
- Lifestyle modifications
- Pharmacologic therapy

- African Americans
  - First line: CCB or thiazides
  - Second line: CCB + thiazide
  - If needed, add ACE Inhibitor or ARB

- Non–African Americans
  - First line: ACE Inhibitor or ARB or CCB or thiazides
  - If needed, add CCB or ACE Inhibitor or ARB or thiazide

**Stage 2 hypertension**
SBP > 160 mm Hg or DBP > 100 mm Hg
- Lifestyle modifications
- Initiate two-drug regimen with ≥1 antihypertensive administered at bedtime

- CCB or thiazide + ACE Inhibitor or ARB
  - If needed, add CCB + thiazide + ACE Inhibitor (or ARB)

If BP is still not controlled after an adequate trial of optimally dosed ACE Inhibitor (or ARB), thiazide diuretic, and CCB, consider adding other agents (e.g., spironolactone, central-acting agents, β-blockers, vasodilators, α-blockers). Avoid combination use of ACE inhibitor and ARB.

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

**Figure 5.** Treatment algorithm for hypertension.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; DBP = diastolic blood pressure; SBP = systolic blood pressure

4. Select appropriate therapy on the basis of the concomitant disease state (Figure 6).

![Initial medication choice based on disease state diagram](image)

**Figure 6.** Selecting appropriate therapy for hypertension on the basis of disease state.


AA = aldosterone antagonist; ACEI = angiotensin-receptor 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, especially with nonselective β-blockers or high-dose selective β-blockers.
      ii. Greater risk of developing DM than with an ACE inhibitor, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity)
      iii. Can mask some signs of hypoglycemia in patients with DM
      iv. Can cause depression
   b. Thiazides
      i. Can worsen gout by increasing serum uric acid
      ii. Not recommended for patients with a CrCl less than 30 mL/minute because of reduced efficacy
      iii. Greater risk of developing DM than with ACE inhibitor, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity)
      iv. Can 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 impairment exists or another K-sparing drug or K supplement is used.
d. Direct renin antagonist (aliskiren)
   i. Contraindicated in pregnancy
   ii. Contraindicated in patients with DM when used in combination with ACE inhibitors or ARBs because of increased risk of renal impairment, hyperkalemia, and hypotension
   iii. Avoid use in combination with cyclosporine oritraconazole.
   iv. Avoid concurrent use with ACE inhibitors or ARBs in patients with renal impairment (CrCl less than 60 mL/minute).

e. Calcium channel blockers
   i. Dihydropyridine CCBs
      (a) Amlodipine, felodipine, nifedipine
      (b) Monitor for peripheral edema, reflex tachycardia, and orthostatic hypotension
      (c) Useful for isolated systolic hypertension or use in African American patients
   ii. Non-dihydropyridine CCBs
      (a) Diltiazem, verapamil
      (b) Indicated in hypertensive patients with comorbid conditions which would benefit from HR reduction (e.g. atrial fibrillation, stable angina)
      (c) Contraindicated in heart block and sick sinus syndrome
      (d) Potential drug interactions due to CYP P450 inhibition

6. Considerations within specific patient populations
   a. Patients with CHD: Potent vasodilators (hydralazine, minoxidil, and DHP CCBs) may cause reflex tachycardia, thereby increasing myocardial oxygen demand; can attenuate this by also using an AV nodal blocker (β-blocker or non-DHP CCB)
   b. Older adult patients:
      i. Caution with antihypertensive agents and orthostatic hypotension
      ii. Initiate with low dose and titrate slowly.
      iii. The SPRINT trial published in late 2015 showed that targeting an SBP of less than 120 mm Hg, compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major CV events and death from any cause among patients at high risk of CV events but without DM. Twenty-five percent of the study population was older than 75 years. This landmark trial may change BP goals in future HTN guidelines.
   c. African American patients: β-Blockers and ACE inhibitors are generally less effective as monotherapy than in non–African American patients; however, combination therapy with thiazides improves effectiveness; β-blockers and ACE inhibitors should still be used if comorbid conditions dictate.
   d. Women
      i. Oral estrogen-containing contraceptives can increase BP, and the risk can increase with the duration of use.
      ii. HTN increases the risk to mother and fetus in women who are pregnant. Preferred medications include methyldopa and labetolol. ACE inhibitors, ARBs, and aliskiren should not be used because of the potential for fetal defects.

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 with optimal dosing (and adherence is verified) and no compelling indication exists, initiate therapy with a drug from a different class while continuing initial therapy.
8. Resistant HTN: Failure to reach goal BP in patients who are prescribed full doses of an appropriate three-drug regimen that includes a diuretic
   a. Causes
      i. Improper BP measurement
      ii. Volume overload
      iii. Excessive Na intake
      iv. Drug-induced causes
         (a) Nonadherence
            (1) Educate patient on the benefits of HTN control. Solicit patient buy-in for BP goals, develop patient-centered treatment strategies, and explain the importance of BP self-monitoring.
            (2) Ensure that regimen is affordable and well tolerated.
            (3) Adjust treatments on the basis of cultural beliefs and attitudes.
            (4) Use all members of the health care team.
         (b) Inadequate doses of antihypertensive medications
         (c) Inappropriate drug combinations
         (d) Specific drugs
            (1) NSAIDs
            (2) Cocaine, amphetamines
            (3) Sympathomimetics
            (4) Oral contraceptives
            (5) Adrenal steroids
            (6) Cyclosporine or tacrolimus
            (7) Erythropoietin
            (8) Licorice
            (9) Dietary supplements
   v. Associated conditions
      (a) Obesity
      (b) Alcoholism
   vi. Identifiable causes of HTN
      (a) Sleep apnea
      (b) Drug-induced or related causes
      (c) CKD
      (d) Primary aldosteronism
      (e) Renovascular disease
      (f) Chronic steroid therapy or Cushing syndrome
      (g) Pheochromocytoma
      (h) Coarctation of the aorta
      (i) Thyroid or parathyroid disease
   b. Treatment: Rule out and/or treat, if possible, causes of resistant HTN.
      i. Administer one or more antihypertensive drug at bedtime for increased efficacy
      ii. For patients with uncontrolled HTN on ACE inhibitor (or ARB) plus thiazide-like diuretic plus CCB, consider adding one (or more) of the following:
         (a) ARA (e.g., spironolactone)
         (b) β-Blocker
         (c) α₁-Blocker
         (d) Vasodilator
         (e) Centrally acting agent
IV. DYSLIPIDEMIA

A. Primary Recommendations
   1. Lifestyle modification is cornerstone of initial intervention.
      a. Heart-healthy diet
         i. Recommend healthy diets such as the Dietary Approaches to Stop Hypertension (DASH) diet or the Mediterranean diet
         ii. Emphasize consumption of fruits, vegetables, whole grains, low-fat dairy products, skinless poultry and fish, nuts and legumes, and nontropical vegetable oils
         iii. Limit sweets, sugar-sweetened beverages, and red meats
         iv. Lower intake of saturated fats and replace with unsaturated fats (especially polyunsaturated fats)
      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 1 of 4 major statin benefit groups

B. Four major statin benefit groups
   1. Patients with clinical atherosclerotic cardiovascular disease (ASCVD). Note that ASCVD includes CHD, stroke or transient ischemic attack, and PAD.
   2. Patients with an LDL-C of 190 mg/dL or greater
   3. Patients with DM age 40–75 years with an LDL-C of 70–189 mg/dL and without ASCVD
   4. Patients age 40–75 years with an LDL-C of 70–189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or greater without DM or ASCVD

C. Recommendations for intensity of statin therapy for ASCVD prevention
Figure 7. Statin intensity recommendations for atherosclerotic cardiovascular disease prevention.

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

D. High-, moderate-, and low-intensity statin doses (Table 17)

<table>
<thead>
<tr>
<th>Patient Group (Age ≥21 years)</th>
<th>Statin recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical ASCVD (coronary heart disease, stroke, and/or peripheral arterial disease)</td>
<td>High-intensity statin (Age ≤75 years)</td>
</tr>
<tr>
<td></td>
<td>Moderate-intensity statin (Age &gt;75 years)</td>
</tr>
<tr>
<td>LDL-C &gt;190</td>
<td>High-intensity statin (Age ≤75 years)</td>
</tr>
<tr>
<td>DM1 or DM2 and age 40-75 years and LDL-C 70-189</td>
<td>Moderate-intensity statin (10-yr ASCVD risk &lt;7.5%)</td>
</tr>
<tr>
<td></td>
<td>High-intensity statin (10-yr ASCVD risk ≥7.5%)</td>
</tr>
<tr>
<td>10-year ASCVD risk ≥7.5% and age 40-75 years and LDL-C 70-189</td>
<td>Moderate-to-high intensity statin</td>
</tr>
<tr>
<td>None of the above</td>
<td>Benefit-to-risk ratio unclear; consider patient-specific factors</td>
</tr>
</tbody>
</table>

Figure 7. Statin intensity recommendations for atherosclerotic cardiovascular disease prevention.

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

D. High-, moderate-, and low-intensity statin doses (Table 17)

Table 17. Relative LDL-C-Lowering Efficacy of Statins

<table>
<thead>
<tr>
<th>Atorva (mg)</th>
<th>Fluva (mg)</th>
<th>Pitava (mg)</th>
<th>Lova (mg)</th>
<th>Prava (mg)</th>
<th>Rosuva (mg)</th>
<th>Simva (mg)</th>
<th>%↓ LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>20–40</td>
<td>1</td>
<td>20</td>
<td>10–20</td>
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<td>10</td>
<td>30</td>
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<tr>
<td>10</td>
<td>80</td>
<td>2</td>
<td>40</td>
<td>40</td>
<td>—</td>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>20</td>
<td>—</td>
<td>4</td>
<td>80</td>
<td>80</td>
<td>5</td>
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<td>—</td>
<td>—</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>47</td>
</tr>
<tr>
<td>80</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20</td>
<td>—</td>
<td>40</td>
<td>55</td>
</tr>
</tbody>
</table>

Denotes high-intensity statin; lowers LDL-C by ≥50%.

Denotes moderate-intensity statin; lowers LDL-C by 30% to <50%.

Denotes low-intensity statin; lowers LDL-C by < 30%.

Atorva = atorvastatin; Fluva = fluvastatin; LDL-C = low-density lipoprotein cholesterol; Lova = lovastatin; Pitava = pitavastatin; Prava = pravastatin; Rosuva = rosuvastatin; Simva = simvastatin.

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. Can be used in patients with type 1 and type 2 DM 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://tools.acc.org/ASCVD-Risk-Estimator/
   a. Sex
   b. Age
   c. Race
   d. TC
   e. HDL-C
   f. SBP
   g. Receiving treatment for high BP
   h. DM
   i. Smoker

F. General approach to initiating statin therapy

1. Check labs
   a. Fasting lipid panel
      i. If LDL-C is higher than 190 mg/dL, evaluate for secondary causes. If primary, screen for familial hypercholesterolemia.
      ii. If TG 500 mg/dL or higher, treat hypertriglyceridemia
   b. Alanine aminotransferase (ALT)
      i. Evaluate patients with unexplained ALT more than 3 x upper limit of normal
   c. Hemoglobin A1c
   d. Creatine kinase (if indicated)
   e. Evaluate for secondary causes or conditions that may affect statin safety

2. Initiate statin therapy based on statin benefit groups in Figure 7.

3. In patients without ASCVD or diabetes, calculate 10-year ASCVD risk using pooled cohort equations
   a. If age 40-75 years and LDL-C 70-189 mg/dL and
      i. ASCVD 10-year risk 5% or higher: engage in discussion with patient regarding ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and patient-specific preferences. Initiate statin therapy (Figure 7) and monitor
      ii. ASCVD 10-year risk less than 5%: select patients may benefit from statins; consider additional factors before making treatment decisions
   b. If age less than 40 years or more than 75 years and LDL-C is less than 190 mg/dL: select patients may benefit from statins; consider additional factors before making treatment decisions
**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 DM, asthma, and a 15 pack-year history of tobacco (quit 3 years ago); she drinks 3 beers per 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%. What is the most appropriate next step for M.M.?

A. Initiate moderate-intensity statin because her 10-year risk is less than 7.5%.
B. Initiate high-intensity statin because her 10-year risk is less than 7.5%.
C. Initiate low-intensity statin because her 10-year risk is less than 7.5%.
D. 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?

A. Pravastatin 20 mg/day.
B. Lovastatin 20 mg/day.
C. Atorvastatin 40 mg/day.
D. Rosuvastatin 10 mg/day.

G. Treatment of patients 21 years and older with LDL-C greater than 190 mg/dL

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

H. Management of very high TG concentrations (greater than 500 mg/dL)

1. Primary goal is to prevent pancreatitis.
2. Weight loss (5%–10% weight loss results in a 20% reduction in TG)
3. Limit sugars and other simple carbohydrates, when possible.
4. Exercise: Aerobic activity at least twice weekly
5. Evaluate for secondary causes. (Table 18)
6. Pharmacologic therapy (Table 19)
   a. Fibrates, omega-3 fatty acids, and niacin will produce largest TG reductions
   b. Statins can also be considered first-line therapy in patients with TG levels of 500–999 mg/dL

<table>
<thead>
<tr>
<th>Table 18. Common Secondary Causes of Elevated LDL-C and TG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Dietary influences</td>
</tr>
<tr>
<td>Disease states and medical conditions</td>
</tr>
</tbody>
</table>

LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.
Table 19. Effect of Lipid-Lowering Medications on TG

<table>
<thead>
<tr>
<th>Medication</th>
<th>% Decrease in TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>7–30</td>
</tr>
<tr>
<td>Fibrates</td>
<td>20–50</td>
</tr>
<tr>
<td>Niacin</td>
<td>20–50</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5–11</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>19–44</td>
</tr>
</tbody>
</table>

TG = triglycerides

I. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)

1. Efficacy
   a. First line for high LDL-C or CHD risk
   b. When selecting a statin, consider its intensity.
   c. Reduce LDL-C by 24%–60%.
   d. Reduce TG by 7%–30%.
   e. Raise HDL-C by 5%–15%.
   f. Reduce major coronary events.
   g. Reduce CHD mortality.
   h. Reduce coronary procedures (percutaneous coronary intervention [PCI] 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 and monitoring
   a. Myopathy (can check creatine kinase [CK] at baseline and then only if muscle symptoms occur; no regular monitoring)
   b. Elevated liver enzymes
      i. Obtain LFTs at baseline in all patients
      ii. Perform repeated LFTs only when clinically indicated.
      iii. Monitor for symptoms of hepatic injury.

4. Absolute contraindications
   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 20)
   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.

6. Differences exist between statins in regard to pharmacokinetics and renal dosing (Tables 21 and 22)
<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Simvastatin</th>
<th>Fluvastatin</th>
<th>Pitavastatin</th>
<th>Atorvastatin</th>
<th>Rosuvastatin</th>
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</thead>
<tbody>
<tr>
<td><strong>Amiodarone</strong></td>
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<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 20 mg</td>
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<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 20 mg</td>
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<td>Daily dose NTE 20 mg</td>
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<td><strong>Cobicistat-containing products</strong></td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
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<tr>
<td><strong>Colesevelam</strong></td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Use with caution</td>
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<tr>
<td><strong>Cyclosporine</strong></td>
<td>Avoid use</td>
<td>Daily dose NTE 20 mg</td>
<td>CI</td>
<td>Daily dose NTE 20 mg BID</td>
<td>CI</td>
<td>Avoid use</td>
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<td><strong>Danazol</strong></td>
<td>Daily dose NTE 20 mg</td>
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<td>CI</td>
<td>CI</td>
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<tr>
<td><strong>Diltiazem</strong></td>
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<td>Daily dose NTE 10 mg</td>
<td>Daily dose NTE 10 mg</td>
<td>Daily dose NTE 10 mg</td>
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<td>Daily dose NTE 10 mg</td>
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<tr>
<td><strong>Dronedarone</strong></td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 10 mg</td>
<td>Daily dose NTE 10 mg</td>
<td>Daily dose NTE 10 mg</td>
<td>Daily dose NTE 10 mg</td>
<td>Daily dose NTE 10 mg</td>
<td>Daily dose NTE 10 mg</td>
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<tr>
<td><strong>Erythromycin</strong></td>
<td>CI</td>
<td>Daily dose NTE 40 mg (clarithromycin)</td>
<td>CI</td>
<td>Daily dose NTE 1 mg (erythromycin)</td>
<td>Daily dose NTE 20 mg (clarithromycin)</td>
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<td><strong>Gemfibrozil</strong></td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>CI</td>
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<td>Avoid use</td>
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<tr>
<td><strong>Grapefruit juice (&gt;1 quart per day)</strong></td>
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<td>Avoid use</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>Avoid excess quantities (&gt;1.2 L/day)</td>
</tr>
<tr>
<td><strong>Fluconazole</strong></td>
<td>CI (itraconazole, ketoconazole, posaconazole, and voriconazole)</td>
<td>CI (itraconazole, ketoconazole, posaconazole, and voriconazole)</td>
<td>CI (itraconazole, ketoconazole, posaconazole, and voriconazole)</td>
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<td>Daily dose NTE 20 mg (itraconazole)</td>
<td>Daily dose NTE 20 mg (itraconazole)</td>
<td>Daily dose NTE 20 mg (itraconazole)</td>
</tr>
<tr>
<td><strong>Lomitapide</strong></td>
<td>Daily dose NTE 20 mg (or 40 mg if tolerated 80 mg for ≥1 yr)</td>
<td>Daily dose NTE 20 mg (or 40 mg if tolerated 80 mg for ≥1 yr)</td>
<td>Daily dose NTE 20 mg (or 40 mg if tolerated 80 mg for ≥1 yr)</td>
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</tr>
<tr>
<td><strong>Nefazodone</strong></td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td><strong>Niacin</strong></td>
<td>Avoid doses of niacin ≥ 1 g/day</td>
<td>Avoid doses of niacin ≥ 1 g/day</td>
<td>Avoid doses of niacin ≥ 1 g/day</td>
<td>Avoid doses of niacin ≥ 1 g/day</td>
<td>Avoid doses of niacin ≥ 1 g/day</td>
<td>Avoid doses of niacin ≥ 1 g/day</td>
<td>Use with caution</td>
</tr>
<tr>
<td><strong>HIV protease inhibitors</strong></td>
<td>CI</td>
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<td>CI</td>
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<td><strong>Ranolazine</strong></td>
<td>Consider dose adjustment</td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 20 mg</td>
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<tr>
<td><strong>Rifampin</strong></td>
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<tr>
<td><strong>Simeprevir</strong></td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 20 mg</td>
</tr>
</tbody>
</table>

CI = contraindicated; HIV = human immunodeficiency virus; NTE = not to exceed.
Table 21. Pharmacokinetic Differences Between Statins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>Half-life (hr)</th>
<th>Elimination/ Metabolism</th>
<th>Prodrug</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>14</td>
<td>14</td>
<td>3A4</td>
<td>No</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>24</td>
<td>3</td>
<td>2C9</td>
<td>No</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>&lt; 5</td>
<td>2-3</td>
<td>3A4</td>
<td>Yes</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>43-51</td>
<td>12</td>
<td>2C9</td>
<td>No</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>17</td>
<td>1.8</td>
<td>N/A</td>
<td>No</td>
<td>Hydrophilic</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>&lt; 5</td>
<td>2</td>
<td>3A4</td>
<td>Yes</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>20</td>
<td>19</td>
<td>2C9</td>
<td>No</td>
<td>Hydrophilic</td>
</tr>
</tbody>
</table>

N/A = not applicable.

Table 22. Dosing of Statin Agents in CKD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
<th>Dose Recommended by KDIGO Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>—</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Doses &gt; 40 mg/day not studied in severe renal impairment</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>CrCl &lt; 30 mL/min: NTE 20 mg/day</td>
<td>Not studied</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>CrCl 15-59: NTE 2 mg/day</td>
<td>2 mg/day</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>CrCl &lt; 30 mL/min: Initial dose = 10 mg/day</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>CrCl &lt; 30 mL/min: Initial dose = 5 mg/day</td>
<td>40 mg/day (ezetimibe/simvastatin 10/20 mg/day)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>CrCl &lt; 30 mL/min: NTE 10 mg/day</td>
<td>10 mg/day</td>
</tr>
</tbody>
</table>


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

CrCl = creatinine clearance; NTE = not to exceed

J. The U.S. Preventive Services Task Force also recommends statin use for primary prevention in select patients.

1. Low- to moderate-dose statins are recommended in adults age 40–75 years without known CV disease (i.e., symptomatic coronary artery disease or history of ischemic stroke) who have at least one CV disease risk factor (dyslipidemia, DM, HTN, or smoking) and a calculated 10-year risk of a CV event of at least 10%.

2. Low- to moderate-dose statins can be considered in adults age 40–75 years without known CV disease who have at least one CV disease risk factor and a calculated 10-year risk of a CV event of 7.5%–10%.

3. Ten-year risk calculations are based on the ACC/AHA Pooled Cohort Equation.

K. Role of nonstatin therapies for LDL-C for statin benefit groups, according to the 2016 ACC Expert Consensus Decision Pathway

1. Factors to consider
   a. Adherence and lifestyle
   b. Statin intolerance
   c. Control of other risk factors
   d. Clinician-patient shared decision making (potential benefits, harms, and preferences)
e. Percentage of LDL-C reduction
f. Monitor response to therapy.

2. Optional interventions to consider
   a. Referral to lipid specialist and/or dietitian
   b. Ezetimibe
   c. Bile acid sequestrants
   d. PCSK9 inhibitors
   e. Mipomersen, lomitapide, or LDL-C apheresis can be considered by lipid specialist for patients with familial hypercholesterolemia.

3. Patients with clinical ASCVD who do not reach goal with statin therapy:
   a. Goal
      i. Greater than 50% LDL-C reduction with statin
      ii. Consider goal LDL-C less than 70 mg/dL or non-HDL-C less than 100 mg/dL
   b. Patients with comorbidities
      i. Add either ezetimibe or PCSK9 inhibitor first
      ii. If insufficient response, add the other agent from item i
   c. Patients without comorbidities
      i. Add ezetimibe first
      ii. If insufficient response, add or replace with PCSK9 inhibitor

4. Patients with a baseline LDL-C 190 mg/dL or higher who do not reach goal with statin therapy:
   a. Goal
      i. Greater than 50% LDL-C reduction with statin
      ii. If known ASCVD, consider goal LDL-C less than 70 mg/dL or non-HDL-C less than 100 mg/dL
      iii. If no ASCVD, consider goal LDL-C less than 100 mg/dL or non-HDL-C less than 130 mg/dL
   b. Add either ezetimibe of PCSK9 inhibitor first
   c. If insufficient response, add the other agent from item a
   d. Consult a specialist for dietician support, specialized medications (e.g. mipomersen, lomitapide), and/or LDL apheresis

5. Patients with DM and no clinical ASCVD who do not reach goal with statin therapy:
   a. Goal
      i. Greater than 50% LDL-C reduction with statin
      ii. Consider goal LDL-C less than 100 mg/dL or non-HDL-C less than 130 mg/dL
   b. Add ezetimibe first
   c. PCSK9 inhibitors not indicated

6. Patients without DM or ASCVD, 40-75 years of age, with LDL-C 70-189 mg/dL and estimated 10-year ASCVD risk 7.5% or higher, on statin
   a. Goal
      i. Thirty to 49% LDL-C reduction with statin
      ii. Consider goal LDL-C less than 100 mg/dL or non-HDL-C less than 130 mg/dL
   b. Add ezetimibe first
   c. PCSK9 inhibitors not indicated

7. In all situations, consider bile acid sequestrant in place of ezetimibe if ezetimibe-intolerant and TG less than 300 mg/dL

L. Bile acid sequestrants (cholestyramine, colestipol, colesvealam)
   1. Efficacy
      a. Reduce LDL-C by 15%–27%.
      b. Raise HDL-C by 3%–5%.
      c. May increase TG concentrations.
d. Reduce major coronary events.
e. Reduce CHD mortality.

2. Mechanism of action: Bind to bile acids to disrupt enterobacterial recirculation of bile acids. Liver is stimulated to convert hepatocellular cholesterol to bile acids.

3. Adverse effects: GI distress, constipation

4. Decreased absorption of many drugs including: warfarin, amiodarone, levothyrerxine, ezetimibe, digoxin, and thiazides; administer drugs 1–2 hours before or 4 hours after bile acid sequestrant

5. Contraindications: Complete biliary obstruction, raised TG concentrations (especially greater than 400 mg/dL)

M. PCSK9 Inhibitors (evolocumab and alirocumab)

1. Efficacy: Lower LDL-C by an additional 45%–68% when combined with statin therapy; evolocumab reduces CV events when added to statin therapy (FOURIER trial)

2. Mechanism of action: Monoclonal antibodies that inhibit a protein called PCSK9, increasing cholesterol clearance from the liver

3. Both indicated for heterozygous familial hypercholesterolemia or clinical ASCVD; evolocumab also indicated for homozygous familial hypercholesterolemia (HoFH)

4. Adverse effects: Injection-site reactions, respiratory infections

5. Dose:
   a. Evolocumab:
      i. Heterozygous familial hypercholesterolemia or clinical ASCVD: 140 mg subcutaneously every 2 weeks or 420 mg subcutaneously once monthly
      ii. Homozygous familial hypercholesterolemia: 420 mg subcutaneously once monthly
   b. Alirocumab: Initial dose, 75 mg subcutaneously every 2 weeks or 300 mg subcutaneously every 4 weeks; if LDL-C reduction inadequate, can adjust dose to 150 mg subcutaneously every 2 weeks

N. Niacin (Table 23)

1. Efficacy
   a. Lowers LDL-C by 5%–25%
   b. Lowers TG by 20%–50%
   c. Raises HDL-C by 15%–35%
   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 synthesis of TG, very-low-density lipoproteins, and LDL-C

3. Adverse effects and monitoring: Flushing, hyperglycemia, hyperuricemia, myopathy, upper GI distress, increased hepatic transaminases; monitor LFTs at baseline, every 6–12 weeks for first year and then yearly

4. Sustained release (appears to be more hepatotoxic than extended-release or immediate-release preparations).

5. Extended-release niacin is less likely to cause flushing.

6. Contraindications: liver disease, active peptic ulcer, arterial hemorrhage. Caution in patients predisposed to gout

7. Flushing can be minimized by taking aspirin or an NSAID 30–60 minutes before niacin, taking at bedtime with food, using slow titration, and avoiding hot beverages, spicy foods, and hot showers around the time of administration. Flush-free formulations (inositol hexanicotinate) do not metabolize into nicotinic acid and therefore do not affect lipids.

8. According to the 2016 ACC nonstatin therapies expert consensus treatment pathway, there are no clear indications for routine niacin use for reduction of LDL-C.
O. Fibrates (fenofibrate, gemfibrozil)
1. Efficacy
   a. Lower LDL-C by 5%–20% (with normal TG)
   b. May raise LDL-C with very high TG
   c. Lower TG by 20%–50%
   d. Raise HDL-C by 10%–20%
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, pre-existing gallbladder disease
5. Recommendations for fibrate use were not included in the 2016 ACC nonstatin therapies expert consensus treatment pathway.

P. Ezetimibe
1. Efficacy
   a. Lowers LDL-C by 18%–20%
   b. Can raise HDL-C by 1%–5%
   c. Lowers TG by 5%–10%
2. Mechanism of action: Inhibition of cholesterol absorption
3. Adverse effects and monitoring: Diarrhea, upper respiratory tract symptoms; no monitoring necessary
4. Data suggest that combination with simvastatin is superior to simvastatin alone in prevention of CV events.

### Table 23. Niacin Formulations

<table>
<thead>
<tr>
<th>Drug Form</th>
<th>Brand Name</th>
<th>Dose Range (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release</td>
<td>Niacin, Niacor</td>
<td>1.5–6</td>
</tr>
<tr>
<td>Extended release</td>
<td>Niaspan</td>
<td>1–2</td>
</tr>
<tr>
<td>Sustained release</td>
<td>Slo-Niacin</td>
<td>1–2</td>
</tr>
</tbody>
</table>

Q. Omega-3 fatty acids
1. Contain varying ratios of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
   a. Omega-3 acid ethyl esters: DHA and EPA
   b. Icosapent ethyl: EPA only
   c. Omega-3 carboxylic acid: DHA and EPA
2. Efficacy
   a. Lowers TG by 26%–45%
   b. Can raise LDL-C when TG concentrations are high
   c. Raises HDL-C by 5%–14%

Patient Case
10. Which best describes a potential secondary cause of high TG concentrations?
   A. Amiodarone.
   B. Biliary obstruction.
   C. Sirolimus.
   D. Saturated fats.
3. Mechanism of action: Reduction of hepatic production of very-low-density lipoproteins; possible reduction in hepatic synthesis of TG; increased hepatic β-oxidation
4. Adverse effects: Arthralgia, GI effects (e.g., burping, taste perversion, dyspepsia); at more than 3 g/day, inhibition of platelet aggregation, bleeding
5. Used to treat hypertriglyceridemia as an adjunct to diet in adults with TG concentrations of 500 mg/dL or greater
6. Dose: 2–4.8 g/day as a single dose or in two divided doses

R. Lomitapide
1. Efficacy: Lowers LDL-C by about 45%
2. Mechanism of action: Selective microsomal TG protein inhibitor
3. Indicated for HoFH
4. Adverse effects and monitoring: Hepatotoxicity, teratogenicity, GI symptoms; monitor LFTs at baseline, then monthly for 1 year (and before increasing dose), then every 3 months (and before increasing dose); female patients also need to have a negative pregnancy test before initiating therapy
5. To reduce incidence of fat-soluble nutrient deficiency, administer daily supplements containing vitamin E (400 units), linoleic acid (≥200 mg), alpha-linolenic acid (≥210 mg), EPA (≥110 mg), and DHA (≥80 mg).
6. Contraindications: Pregnancy, concurrent use of moderate or strong CYP3A4 inhibitors, moderate or severe hepatic disease
7. Drug interactions
   a. Major CYP 3A4 substrate
   b. Contraindicated with moderate and strong CYP 3A4 inhibitors. Do not exceed 30 mg daily when used concomitantly with weak CYP 3A4 inhibitors (e.g., atorvastatin, oral contraceptives).
   c. Limit simvastatin doses to 20 mg daily (or 40 mg in patients who previously tolerated simvastatin 80 mg daily for ≥1 year). Although the interaction between lomitapide and lovastatin has not been studied,Lovastatin and simvastatin metabolism is similar, andLovastatin dose reductions should be considered.
8. Available only through the Risk Evaluation and Mitigation Strategy (REMS) program
9. Dose: 5 mg once daily, can be titrated to 60 mg/day

S. Mipomersen
1. Efficacy: Lowers LDL-C by about 25%
2. Mechanism of action: Oligonucleotide targeted to human messenger RNA, reducing formation of ApoB, the main component of LDL-C
3. Indicated for HoFH
4. Adverse effects and monitoring: Hepatotoxicity, flulike symptoms, injection site reactions, antibody development; monitor LFTs at baseline, then monthly for 1 year and then every 3 months
5. Contraindications: Moderate or severe hepatic disease
6. Available only through the REMS program
7. Dose: 200 mg subcutaneously once weekly

V. CHRONIC CORONARY HEART DISEASE AND CHRONIC STABLE ANGINA

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 DM  
E = Education and exercise

Although not all patients with CHD have DM 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 and maintenance to a body mass index of 18.5–24.9 kg/m² and a waist circumference less than 40 inches for male patients and less than 35 inches for female patients
- Physical activity for 30–60 minutes/day, 7 days/week (minimum of 5 days/week)
- BP less than 140/90 mm Hg
- Alcohol consumption should be limited to 1 drink (120 mL [4 ounces] of wine, 360 mL [12 ounces] of beer, or 30 mL [1 ounce] 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 a patient has DM, A1C less than 7%; a goal A1C of 7%–9% is reasonable in certain patients according to age, history of hypoglycemia, presence of microvascular or macrovascular complications, or comorbid conditions.
- Annual influenza vaccine

Patient Case

11. A 66-year-old man with a medical history of HTN and acute coronary syndrome with a drug-eluting coronary stent placement 14 months ago presents to the primary care clinic. Current medications include aspirin 81 mg/day, prasugrel 10 mg/day, nitroglycerin 0.4-mg sublingual tablets as needed for chest pain, metoprolol succinate 75 mg/day, ramipril 10 mg/day, and atorvastatin 20 mg/day. He asks you how long he will need to take prasugrel. What is the best answer?
   A. Call your physician because you may be able to stop prasugrel now.
   B. Your prasugrel should have been discontinued 6 months after acute coronary syndrome; discontinue it now.
   C. You will need to take prasugrel indefinitely.
   D. You will need to take prasugrel for at least 18 months after your MI and stent placement.

Therapeutic Management of CHD

A. Aspirin for Stable CHD
   1. Indicated in all patients with CHD unless contraindicated
   2. Dose: 75–162 mg/day
   3. Decreases CV events by about one third
   4. Clopidogrel 75 mg/day can be used if aspirin contraindicated (e.g., allergy)
B. Antiplatelet therapy for stable CHD for patients undergoing PCI (Table 24)

Table 24. Recommendations for Dosing and Duration of Antiplatelet Therapy in SIHD

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Aspirin</th>
<th>P2Y&lt;sub&gt;12&lt;/sub&gt; Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Dose</td>
<td>Subsequent Doses (Starting Day 2) and Therapy Duration</td>
</tr>
<tr>
<td>SIHD treated with PCI and BMS placed</td>
<td>325 mg before PCI</td>
<td>75–100 mg/day indefinitely</td>
</tr>
<tr>
<td>SIHD treated with PCI and DES placed</td>
<td>325 mg before PCI</td>
<td>75–100 mg/day indefinitely</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Class I recommendation; defined as “should be given.”

<sup>b</sup>Class IIb recommendation; defined as “may be considered.”

<sup>c</sup>Each patient should be evaluated for his or her individual ischemic/bleeding risk, preferences, cost, etc., to determine the ideal duration of dual antiplatelet therapy.

<sup>d</sup>The DAPT Score detailed in Cardiology I may be used to guide decisions regarding thrombotic versus bleeding risk

BMS = bare metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease.


C. Lipid-lowering therapy (see section IV: Dyslipidemia)
   1. Counsel on healthy lifestyle habits
   2. Lipid panel, baseline alanine aminotransferase; consider secondary causes of dyslipidemia, evaluate for conditions that may influence statin safety
   3. High-intensity statin therapy if without contraindications, drug–drug interactions, advanced age, or history of statin intolerance (class I recommendation)

D. ACE Inhibitors
   1. Greatly decrease CV events in patients with CHD (and no left ventricular 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, DM, and/or CKD (class I recommendation)
   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 (class IIb recommendation).

E. ARBs: Recommended as an alternative to ACE inhibitors in patients who also have an LVEF of 40% or less, HTN, DM, or CKD or who are unable to tolerate an ACE inhibitor (e.g., cough or angioedema; class IIa recommendation)
F. 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. Goal exercise HR of no more than 75% HR associated with angina symptoms
      iv. Place in therapy: May be considered chronic therapy for all patients with coronary or other vascular disease. Should be prescribed first-line for relief of angina symptoms in patients with stable ischemic heart disease (class I). Also a class I indication for first 3 years post-MI
      v. Contraindications: Severe bradycardia (HR less than 50 beats/minute), high-degree AV block or sick sinus syndrome (in absence of a pacemaker)
   b. CCBs
      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) Non-DHP CCBs may be added to β-blocker therapy to achieve HR goals (caution advised; combination can cause heart block).
         (b) Instead of β-blocker therapy when unacceptable adverse effects emerge or if treating Prinzmetal’s angina
         (c) Short-acting CCBs (nifedipine) have been associated with increased CV events; should be avoided (except in slow-release formulations)
      iii. Contraindications for non-DHP CCBs: HF/EF, severe bradycardia, high-degree AV block or sick sinus syndrome (in absence of a pacemaker)
      iv. Contraindications for DHP CCBs: HF/EF (except amlodipine and felodipine)
   c. Nitrates
      i. Pharmacologic effects:
         (a) Endothelium-dependent vasodilation, dilates epicardial arteries and collateral vessels (increase oxygen supply)
         (b) Decreased left ventricular volume because of decreased preload mediated by venodilation (decrease oxygen demand)
      ii. Place in therapy
         (a) A scheduled long-acting nitrate is useful in conjunction with a β-blocker or non-DHP CCB, or both (to blunt the reflex sympathetic tone with nitrate therapy).
         (b) As-needed sublingual tablets, powder, or spray nitroglycerin is necessary to relieve effort or rest angina.
         (c) In addition, as-needed sublingual tablets, powder, or spray nitroglycerin can be used before exercise to avoid ischemic episodes.
      iii. Caution: Hypertrophic obstructive cardiomyopathy, inferior wall MI, severe aortic valve stenosis, avanafil within 12 hours, sildenafil and vardenafil within 24 hours, tadalafil within 48 hours
d. Ranolazine
   i. Pharmacologic effects
      (a) Inhibits the late phase of the inward Na channel in ischemic myocytes during repolarization, leading to a reduction in intracellular Na concentrations. This reduction in Na concentrations leads to reduced calcium influx, which decreases ventricular tension and myocardial oxygen consumption.
      (b) Increases “oxygen efficiency”
   ii. Place in therapy
      (a) Ideal role is unclear
      (b) Use in combination with β-blockers, CCBs, or nitrates when initial management with these drugs is unsuccessful.
      (c) Use when BP or HR is too low to add β-blockers, CCBs, or nitrates
      (d) Important points
         (1) No significant effects on HR or BP; thus, bradycardia and hypotension are not of concern
         (2) Dose-related QT interval prolongation
         (3) Metabolized by CYP3A; P-gp substrate
            (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, carbamazepine, or St. John’s wort.
            (D) Limit the dose to 500 mg twice daily in patients receiving moderate CYP3A4 inhibitors, including diltiazem, verapamil, erythromycin, fluconazole, and grapefruit juice.

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REFERENCES

Heart Failure

Atrial Fibrillation

Hypertension


Dyslipidemia


CHD and Chronic Stable Angina


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A
This patient has NYHA class III HFpEF with an LVEF of 20%. The best option is to increase her carvedilol dose to the goal dose of 25 mg twice daily (Answer A). Despite her heart rate of 68 beats/minute, it is safe to increase the β-blocker. Higher carvedilol doses have been associated with reductions in mortality. Appropriate monitoring would include signs and symptoms of hypotension and bradycardia. Her ACE inhibitor is already at the maximum recommended lisinopril dose for heart failure; therefore, further increases are not warranted (Answer B). Spironolactone 25 mg/day is the recommended dose for patients with HFpEF who are already receiving an ACE inhibitor and a β-blocker and are NYHA class III. Increasing the spironolactone dose to 50 mg/day is unwarranted (Answer C). Her digoxin concentration of 0.7 ng/dL is within the desired range of 0.5–0.9 ng/mL; therefore, no dose 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 blood pressure of 120/70 mm Hg safely permits increasing enalapril from 5 to 10 mg twice daily, making Answer B correct. The patient’s SCr does not prevent the enalapril dose from being titrated because it is stable, and he does not have hyperkalemia. 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 (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 nodal blockade is warranted with either a non-dihydropyridine 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 CHA₂DS₂-VASc score of 3; therefore, anticoagulation with an oral anticoagulant agent is indicated. Warfarin titrated to a goal INR of 2.5 would be a potentially appropriate option; however, this patient may be unable to travel to his primary care provider’s office for weekly INR checks (Answer C). 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 impairment.

5. Answer: C
With the new diagnosis of HFpEF, this patient can no longer receive sotalol. Discontinuing this medication is 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 Answers A and D incorrect. If rhythm control is desired, amiodarone and dofetilide are the only two antiarrhythmic drugs that have been proved safe and effective in patients with HFpEF, 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’s goal BP is less than 140/90 mm Hg, and this is a compelling reason to have a β-blocker as part of his antihypertensive regimen. In general, African American patients do not respond as well as white patients do 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 (Answers C and D) or diltiazem (Answer A) is inferior to β-blockade in this patient population.

7. Answer: C
For adults both with and without DM having a urine albumin excretion of at least 30 mg/24 hour (or equivalent) and whose BP is consistently greater than 130/80 mm Hg, the BP target is less than 130/80 mm Hg. The presence of DM 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 mildly elevated BP (Answer C). Although amlodipine (Answer B) could get the patient to her goal BP, it 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 because of the presence of microalbuminuria.

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 DM (Answer A), and her 10-year risk of ASCVD is 7.5% or less. Because she has a 10-year ASCVD risk of 7.5% or less, she is not a candidate for a high-intensity statin (Answer B), despite having DM. Because she has DM, low-intensity statin therapy is not recommended (Answer C). If she did not have DM, 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 could be recalculated in 4–6 years.

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

10. Answer: C
If fasting TG concentrations are 500 mg/dL or greater or LDL-C is greater than 190 mg/dL, patients should be assessed for potential secondary causes of their dyslipidemia. Secondary causes of elevated TG include high intake of carbohydrates, excessive alcohol intake, oral estrogens, glucocorticoids, protease inhibitors, sirolimus (Answer C), thiazides, anabolic steroids, rapamycin, β-blockers, nephrotic syndrome, CKD, lipodystrophies, poorly controlled DM, hypothyroidism, pregnancy, and obesity. Amiodarone (Answer A), biliary obstruction (Answer B), and saturated fats (Answer D) are all secondary causes of increased LDL-C.

11. Answer: A
After placement of a drug-eluting stent for acute coronary syndrome, a P2Y12 inhibitor is indicated for 12 months for most patients; therefore, Answer A is correct. Answer B is incorrect because 6 months of dual antiplatelet therapy is only for patients at high risk of bleeding, and there is no indication that this patient is at high risk of bleeding. No current data support dual antiplatelet therapy indefinitely; therefore, Answer C is incorrect. Answer D is incorrect because the guidelines recommend dual antiplatelet therapy for at least 12 months, not 18 months, in most patients.
ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D
This patient has HFpEF (NYHA class III), probably secondary to her MI 4 months ago, and is not receiving optimal HF therapy with an ACE inhibitor and β-blocker, making Answer A incorrect. ACE inhibitors are considered the cornerstone of therapy for HFpEF because evidence shows 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 HFpEF, unless there is a contraindication. 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 not symptomatic and is not receiving optimal therapy. Although the patient is NYHA class III, no rationale exists for adding spironolactone at this time because she is not receiving 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. Adding 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 Answers A and D incorrect.

3. Answer: A
This patient has HFpEF, which is caused by a problem with ventricular relaxation. The preferred therapy is either a β-blocker or a non-dihydropyridine CCB, each of which slows the HR and permits the ventricle greater time to fill with blood. Diltiazem, a non-DHP 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 HFpEF, they can be considered in HFpEF if further antihypertensive therapy is needed after the HR is decreased (Answer D).

4. Answer: D
This patient’s CHA₂DS₂-VASc score is 4 (risk factors are HTN, PAD, and age greater than 75 years), making him a candidate for an oral anticoagulant, such as warfarin, because of his AF. Use of an oral anticoagulant will greatly decrease his risk of stroke from about 5% per year to about 1% per year. Because his HR is less than 110 beats/minute with atenolol therapy, there is no reason to discontinue atenolol. In addition, there is no reason to add an additional rate control drug, such as digoxin (Answer B) or diltiazem (Answer A). With his PAD, atorvastatin therapy is necessary, making Answer C incorrect. In addition, his BP is well controlled; therefore, increasing the lisinopril dose is not warranted, making Answer B incorrect. To derive the beneficial antiplatelet effects for CV event prevention, aspirin 81 mg is adequate. Aspirin 325 mg/day 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 a bad choice (Answer D). 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

According to the JNC8 guidelines, this patient’s SBP goal is less than 120 mm Hg because he is at least 60 years old. Given that he is already taking two medications to control his BP, further intensification to an SBP of less than 140 mm Hg could be considered, but given his age (82 years) and his SBP (145 mm Hg), the patient is within goal, making Answer D correct and Answers A and C incorrect. According to current guidelines, 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 losinorpril from 40 to 80 mg is unlikely to achieve a significant degree of BP lowering.

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 with an LDL-C of 70–189 mg/dL and a 10-year ASCVD risk of 7.5% or greater without DM or ASCVD) 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 TG concentrations 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 because his TG concentrations are lower than 500 mg/dL (Answer C). Rosuvastatin 2.5 mg is a low-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. According to the cholesterol guidelines, patients who are 40–75 years old, without ASCVD or DM, and have an LDL-C of 70–189 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 hypertriglyceridermia should be ruled out when TG concentrations 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 values. Although obesity, poorly controlled DM, olatrazapine, and metoprolol can increase TG concentrations, coenzyme Q does not affect TG; therefore, Answer A is incorrect. Alcohol consumption, poorly controlled DM, and β-blockers can all increase TG, but weight loss does not increase TG. Weight loss can actually lower LDL-C and TG; therefore, Answer B is incorrect. All the choices in Answer C can increase TG, making Answer C incorrect. All the conditions, medications, or disease states in Answer D can increase TG, making this option correct.

10. Answer: D

Oral contraceptives, specifically estrogen, can increase BP, especially with a longer duration of use. An alternative contraceptive without estrogen would be less likely to contribute to her HTN (Answer D is correct). Answers A and B are incorrect because her BP requires better control, but weight loss is unlikely to help because her BMI is normal. Answer C is incorrect because hydrochlorothiazide is no more potent than chlorothalidone.

11. Answer: B

ACE inhibitor therapy is contraindicated in pregnancy, and discontinuing ramipril is the most important next step, making Answers A and C incorrect. Answer D is incorrect because this patient will require good BP control during her pregnancy. Labetalol is a good choice of therapy because it is a preferred antihypertensive drug in pregnancy (Answer B is correct).
12. **Answer: D**

Because the patient has CHD, his options for antiarrhythmic therapy are limited. Class Ic antiarrhythmic drugs are contraindicated in patients with CHD; therefore, flecainide and propafenone cannot be used (Answers B and C are incorrect). Disopyramide, a class Ia antiarrhythmic, is not a preferred therapy for AF; therefore, Answer A is incorrect. Sotalol, a class III antiarrhythmic, can be used in patients with CHD and good renal function; therefore, Answer D is correct.