Cardiology II

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CARDIOLOGY II

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SOUTH CAROLINA COLLEGE OF PHARMACY
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Learning Objectives

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

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 artery disease (CAD) (myocardial infarction [MI] 4 months ago), and dyslipidemia, presents to the clinic for follow-up. She is without complaints and has no worsening signs or symptoms of dyspnea or edema compared with her baseline. An echocardiogram reveals a left ventricular ejection fraction (LVEF) of 35%. She is New York Heart Association (NYHA) class III. Her medications include aspirin 81 mg/day, metoprolol succinate 150 mg/day, and simvastatin 20 mg every night. Her vital signs include heart rate (HR) 58 beats/minute and blood pressure (BP) 138/80 mm Hg. Her lungs are clear, and laboratory results are within normal limits. Given her history and physical examination, which is the most appropriate modification to R.S.’s current drug therapy?
   A. Continue current therapy.
   B. Initiate spironolactone 25 mg/day.
   C. Initiate lisinopril 5 mg/day.

2. J.O. is a 64-year-old woman with NYHA class II nonischemic dilated cardiomyopathy (LVEF of 30%). She presents to the heart failure (HF) clinic for follow-up. She has no complaints. Her medications include enalapril 10 mg twice daily, furosemide 40 mg twice daily, and potassium chloride 20 mEq twice daily. Her vital signs include BP 130/88 mm Hg and HR 78 beats/minute. Her laboratory results are within normal limits. Which would be the best option to further manage J.O.’s HF?
   A. Continue current regimen.
   B. Increase enalapril to 20 mg twice daily.
   C. Initiate carvedilol 3.125 mg twice daily.
   D. Initiate digoxin 0.125 mg/day.

3. J.M. is a 65-year-old woman with a history of HTN and poor medication adherence who presents to her primary care physician with shortness of breath and markedly decreased exercise tolerance. An echocardiogram reveals an LVEF of 65% with considerable diastolic dysfunction. J.M.’s medications include extended-release nifedipine 90 mg/day and hydrochlorothiazide 25 mg/day. Her vital signs include BP 128/78 mm Hg and HR 98 beats/minute. Her lung fields are clear to auscultation, and there is no evidence of systemic congestion. Which is the best pharmacologic management for J.M.?
   A. Discontinue extended-release nifedipine, and initiate diltiazem 240 mg/day.
   B. Discontinue hydrochlorothiazide, and initiate furosemide 40 mg twice daily.
   C. Initiate digoxin 0.125 mg/day.
   D. Add lisinopril 5 mg/day.

4. B.W. is a 78-year-old man with a history of HTN, peripheral arterial disease (PAD), gastroesophageal reflux disease, and atrial fibrillation (AF) for the past month. His therapy includes aspirin 325 mg/day, lansoprazole 30 mg every night, atenolol 50 mg/day, lisinopril 10 mg/day, and atorvastatin 20 mg/day. His vital signs include BP 132/72 mm Hg and HR 68 beats/minute. Which is the best therapy for B.W. at this time?
   A. Add diltiazem and warfarin.
   B. Add digoxin and increase lisinopril to 20 mg/day.
   C. Discontinue atorvastatin and add warfarin.
D. Add warfarin and decrease aspirin to 81 mg/day.

5. Z.G. is a 61-year-old man with AF, HTN, and hypercholesterolemia. His medications include digoxin 0.125 mg/day, warfarin 5 mg/day, amlodipine 10 mg/day, and pravastatin 20 mg every night. He comes to the clinic today with no complaints except for palpitations and shortness of breath when doing yard work. His vital signs include BP 138/80 mm Hg and HR 100 beats/minute. All laboratory results are within normal limits; his international normalized ratio (INR) is 2.4, and his digoxin concentration is 1.1 ng/dL. Which is the best option to help with Z.G.’s symptoms?
   A. Add metoprolol succinate 50 mg/day.
   B. Increase digoxin to 0.25 mg/day.
   C. Continue current regimen; advise the patient to avoid activities that cause symptoms.
   D. Add verapamil 240 mg/day.

6. R.P. is an 82-year-old African American man with a history of HTN, transient ischemic attack (TIA), and gout. His medications include allopurinol 300 mg/day, amlodipine 10 mg/day, lisinopril 40 mg/day, and aspirin 81 mg/day. His vital signs include BP 145/85 mm Hg and HR 82 beats/minute. Which is the best approach to improve R.P.’s BP control?
   A. Add hydrochlorothiazide 25 mg/day to achieve a systolic BP goal of less than 150 mm Hg.
   B. Increase lisinopril to 80 mg/day and titrate to achieve a systolic BP goal of less than 130 mm Hg.
   C. Add atenolol 50 mg/day to achieve a systolic BP less than 140 mm Hg.
   D. Make no changes to his current medications because his systolic BP is at goal.

7. J.T. is a 58-year-old man who presents to his primary care provider for the first time in 10 years. He has been a 2 pack/day smoker for the past 30 years and takes no medication. A fasting lipid panel shows total cholesterol (TC) 222 mg/dL, low-density lipoprotein cholesterol (LDL-C) 105 mg/dL, triglycerides (TG) 330 mg/dL, and high-density lipoprotein cholesterol (HDL-C) 51 mg/dL. His vital signs include BP 140/75 mm Hg and HR 80 beats/minute. His Pooled Cohort equation reveals a 10-year ASCVD risk of 14.6%. According to his risk, which would be the best pharmacologic therapy to initiate in J.T.?
   A. Initiate simvastatin 20 mg once daily and gemfibrozil 600 mg twice daily.
   B. Initiate rosuvastatin 5 mg once daily.
   C. Initiate pravastatin 20 mg once daily and fenofibrate 160 mg once daily.
   D. Initiate atorvastatin 40 mg once daily.

8. R.K. is a 67-year-old man with chronic stable angina. He has had worsening chest discomfort with exercise and has been using his as-needed nitroglycerin with increasing frequency. His medications include aspirin 81 mg/day, atenolol 100 mg/day, atorvastatin 80 mg/day, and lisinopril 20 mg/day. Today, his vital signs include BP 136/80 mm Hg and HR 60 beats/minute. His lipid panel is TC 151 mg/dL, TG 58 mg/dL, HDL-C 68 mg/dL, and LDL-C 68 mg/dL. During exercise, his HR typically increases to 85 beats/minute. Which would be the best option to improve his anginal symptoms?
   A. Add amlodipine 5 mg/day.
   B. Discontinue atenolol and begin extended-release nifedipine 90 mg/day.
   C. Add clopidogrel 75 mg/day.
   D. Add ezetimibe 10 mg/day.

9. 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 coronary heart disease (CHD). His only medication is lisinopril 10 mg once daily. His BP is 145/90 mm Hg. A fasting lipid profile is obtained that reveals TC 238 mg/dL, TG 95 mg/dL, LDL-C 176 mg/dL, and HDL-C 43 mg/dL. His calculated 10-year risk according to the Pooled Cohort Equation is 3.9%. According to his history and calculated 10-year risk, which best describes the next step for management in J.S.?
   A. Initiate high-intensity statin therapy.
   B. Do not initiate statin therapy, and reevaluate risk in 1–3 years.
   C. Initiate moderate-intensity statin therapy.
   D. Do not initiate statin therapy, and reevaluate risk in 4–6 years.
10. J.C. is a 62-year-old man (weight 135 kg [1 month ago 143 kg], height 178 cm) with a history of diabetes, chronic renal insufficiency, bipolar disorder, CAD, and hypertriglyceridemia that, in the past, has resulted in pancreatitis. His family history is significant for his father having CAD and hypertriglyceridemia. He is not a smoker but admits drinking a 6-pack of beer daily. Pertinent laboratory findings include a hemoglobin A1C (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. Which best describes potential secondary causes of elevated TG that should be considered in J.C.?

A. Obesity, poorly controlled diabetes, olanzapine, metoprolol, coenzyme Q10.

B. Alcohol consumption, poorly controlled diabetes, weight loss, β-blockers.

C. Obesity, alcohol consumption, β-blockers, olanzapine, biliary obstruction.

D. Alcohol consumption, obesity, poorly controlled diabetes, olanzapine, metoprolol.
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 20 mg/day, furosemide 40 mg twice daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day. She has been stable on these doses for the past month. Her most recent laboratory results include the following: sodium (Na) 140 mEq/L, potassium (K) 4.0 mEq/L, chloride 105 mEq/L, bicarbonate 26 mEq/L, blood urea nitrogen (BUN) 12 mg/dL, Scr 0.8 mg/dL, glucose 98 mg/dL, calcium 9.0 mg/dL, phosphorus 2.8 mg/dL, magnesium (Mg) 2.0 mEq/L, and digoxin 0.7 ng/mL. Her vital signs today include BP 112/70 mm Hg and HR 68 beats/minute. Which is the best approach for maximizing the management of her HF?
   A. Increase carvedilol to 25 mg twice daily.
   B. Increase lisinopril to 40 mg/day.
   C. Increase spironolactone to 50 mg/day.
   D. Increase digoxin to 0.25 mg/day.

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

A. Background: Heart failure (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. HF with reduced ejection fraction (HFrEF) or systolic dysfunction
   a. Defined as a clinical diagnosis of HF and a left ventricular ejection fraction (LVEF) of 40% or less
   b. Dilated ventricle
   c. Two-thirds of cases are attributable to coronary heart disease (CHD).
   d. One-third of cases are attributable to nonischemic cardiomyopathy.
      i. Hypertension
      ii. Thyroid disease
      iii. Obesity
      iv. Stress (takotsubo)
      v. Cardiotoxins
         (a) Alcohol
         (b) Chemotherapeutic agents
            (1) Anthracyclines
            (2) Cyclophosphamide (high dose)
(3) Fluorouracil
(4) Trastuzumab
(c) Cocaine
vi. Myocarditis
vii. Idiopathic
viii. Tachycardia
ix. Peripartum

2. Heart failure with preserved EF (HFrEF) or diastolic dysfunction
   a. Defined as an LVEF of 50% or greater
   b. Accounts for about 30% (highly variable) of patients with HF
   c. Impaired ventricular relaxation and filling
   d. Normal wall motion
   e. Most common cause is HTN (60%–89%).

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

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

Table 1. HF Failure Stages and Corresponding NYHA Functional Class

<table>
<thead>
<tr>
<th>Stage</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At high risk of HF but without structural heart disease or symptoms of HF • Patients with hypertension, atherosclerotic disease, diabetes mellitus, obesity, or metabolic syndrome OR patients using cardiotoxins or having a family history of cardiomyopathy</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but without signs or symptoms of HF • Patients with a previous MI, left ventricular remodeling, left ventricular hypertrophy, or asymptomatic valvular disease</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with prior or current symptoms of HF • Patients with known structural heart disease and shortness of breath, fatigue, and/or reduced exercise tolerance</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions • Patients who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)</td>
</tr>
</tbody>
</table>

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

HFrEF or Systolic Failure

B. Pharmacologic Therapy
   1. Diuretics (class I indication)
      a. Place in therapy: Indicated in patients with evidence of fluid retention
      b. Short-term benefit (days)
         i. Decreased jugular venous distension
         ii. Decreased pulmonary congestion
         iii. Decreased peripheral edema
      c. Intermediate-term benefits (weeks to months)
         i. Decreased daily symptoms
         ii. Increased exercise tolerance
      d. Long-term benefits (months to years): No benefit on mortality
      e. Mechanism of action: Inhibits reabsorption of Na in the ascending limb of the loop of Henle (loops)
         or in the distal tubule (thiazides)
      f. Dosing and administration considerations
         i. Not to be used as monotherapy for HF because these agents have no effect on disease
            progression or mortality. Should be combined with an angiotensin-converting enzyme (ACE)
            inhibitor, β-blocker, and aldosterone antagonist
         ii. Start with a low initial dose; may then double the dose and titrate according to the patient’s
            weight and diuresis. Note that differences exist in the bioavailability of oral doses.
         iii. If a patient has fluid overload, initiate and adjust therapy to result in 1–2 lb of weight loss per
            day (may be more aggressive in the inpatient setting).
         iv. Chronic therapy should be adjusted to maintain a euvolemic state.
         v. May combine with another diuretic class (e.g., thiazide diuretic) for synergy, if needed
         vi. Monitor and replace K and Mg as needed, especially with loop diuretics (goal with CV
            disease is K of 4.0 mEq/L or greater and Mg of 2.0 mEq/L or greater to minimize the risk of
            arrhythmias).
      vii. Loop diuretics are preferred because of their greater diuretic capabilities; loop diuretics also
           retain efficacy with decreased renal function.
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>Loop Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>10–67</td>
<td>20–40 mg once or twice daily</td>
<td>600</td>
<td>6–8</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>80–100</td>
<td>0.5–1 mg once or twice daily</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</td>
<td>100</td>
<td>25–50 mg once or twice daily</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Thiazide Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>65–75</td>
<td>25 mg once or twice daily</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</td>
<td>30–50</td>
<td>250–500 once or twice daily</td>
<td>2000</td>
<td>6–12</td>
</tr>
</tbody>
</table>

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

bAvailable in oral and intravenous formulations.

2. ACE inhibitors (class I indication)
   a. Place in therapy: Recommended in all patients with HFrEF and current or prior symptoms, unless contraindicated
   b. Benefits
      i. Decreased mortality (about 25%–50% relative risk reduction vs. placebo depending on severity of HF)
      ii. Decreased hospitalizations (about 30% relative risk reduction vs. placebo)
      iii. Symptom improvement
      iv. Improved clinical status
      v. Improved sense of well-being
   c. Mechanism of action
      i. Blocks production of angiotensin II
         (a) Decreases sympathetic stimulation
         (b) Decreases production of aldosterone and vasopressin
         (c) Decreases vasoconstriction (afterload and preload)
      ii. Increases bradykinins (decreases their metabolism)
         (a) Increases vasodilatory prostaglandins
         (b) May affect myocardial remodeling
   d. Dosing and administration considerations
      i. Start low and double the dose every 1–4 weeks to target dose.
      ii. Compared with patients with systolic dysfunction who received low-dose lisinopril (2.5–5 mg/day), patients who received high-dose lisinopril (32.5–35 mg/day) had no difference in all-cause mortality or CV mortality but did have a significant 12% lower risk of death or hospitalization for any reason and 24% fewer hospitalizations for HF.
iii. Patient may notice symptom improvement in several weeks.
iv. Avoid use in patients who have experienced angioedema or if they are pregnant or plan to become pregnant.
v. Use caution if systolic BP is less than 80 mm Hg, SCr is greater than 3 mg/dL, or elevated K is greater than 5.0 mEq/L; use caution in bilateral renal artery stenosis.
e. Monitoring: SCr and K 1–2 weeks after starting or increasing the dose, especially in high-risk individuals (preexisting hypotension, diabetes, K supplements, azotemia)
i. SCr may rise (up to a 20% increase is acceptable) because of renal efferent artery dilation (results in a slightly decreased glomerular filtration rate). Rarely, acute renal failure occurs, especially if the patient is intravascularly depleted (be careful to avoid overdiuresis).
ii. Monitor BP and symptoms of hypotension (e.g., dizziness, light-headedness).
   a. BP may be low to begin with because of low CO.
   b. BP = CO × SVR, where CO = cardiac output and SVR = systemic vascular resistance.
   c. In HF, as CO increases because of decreased SVR, BP may decrease slightly or remain the same.
   d. Symptoms of hypotension are often not present with small dose increases. Remember to treat the patient, not the number.
iii. 90% of people tolerate ACE inhibitors.
   a. Angioedema (less than 1%)—May switch to angiotensin II receptor blockers (ARBs; cross-reactivity is 2.5%) or hydralazine–isosorbide dinitrate
   b. Cough (20%)—May switch to ARBs (less than 1%)

Table 3. ACE Inhibitors and Recommended Dosing

<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 tid</td>
<td>50 mg tid</td>
<td>50 mg tid</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg bid</td>
<td>10 mg bid</td>
<td>20 mg bid</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–5 mg/day</td>
<td>20 mg/day</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg/day</td>
<td>8 mg/day</td>
<td>16 mg/day</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–2.5 mg/day</td>
<td>10 mg/day</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg/day</td>
<td>4 mg/day</td>
<td>4 mg/day</td>
</tr>
</tbody>
</table>

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

3. Angiotensin receptor blockers (ARBs) – 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)
b. Have not been proven superior to ACE inhibitors at target HF dosages
c. 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
d. May be considered in addition to an ACE inhibitor if persistently symptomatic and already taking an ACE inhibitor and a β-blocker but only when an aldosterone antagonist is not tolerated or indicated
e. Possibly considered if patient has experienced ACE inhibitor–induced angioedema
f. Do not combine with an ACE inhibitor and an aldosterone antagonist because this may be harmful.
Table 4. ARBs and Recommended Dosing

<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/day</td>
<td>32 mg/day</td>
</tr>
<tr>
<td>Losartan</td>
<td>25–50 mg/day</td>
<td>150 mg/day</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20–40 mg bid</td>
<td>160 mg bid</td>
</tr>
</tbody>
</table>

ARB = angiotensin receptor blocker; bid = twice daily.

4. β-Blockers
   a. Place in therapy
      i. Recommended in all patients with HFrEF with current or prior symptoms unless contraindicated (class I indication)
      ii. Benefits of β-blockade (when added to an ACE inhibitor)
          a) Decreased mortality (about 35% relative risk reduction vs. placebo)
          b) Decreased hospitalizations (about 25% relative risk reduction vs. placebo)
          c) Symptom improvement
          d) Improved clinical status
          e) Produce greater symptom improvement and reduction in the risk of death at higher doses than ACE inhibitors
   b. Mechanism of action
      i. Blocks the effect of norepinephrine and other sympathetic neurotransmitters on the heart and vascular system
         a) Decreases ventricular arrhythmias (sudden cardiac death)
         b) Decreases cardiac hypertrophy and cardiac cell death
         c) Decreases vasoconstriction and HR
      ii. Carvedilol also provides α₁-blockade.
         a) Further decreases SVR (afterload)
         b) Results in greater reduction in BP than metoprolol succinate
   c. Dosing and administration considerations
      i. Only bisoprolol, carvedilol, or sustained-release metoprolol succinate are recommended in HFrEF.
      ii. Add to existing ACE inhibitor therapy (at least at a low dose) when HF symptoms are stable and patients are euvoletic.
      iii. Should not be prescribed without diuretics in patients with current or recent history of fluid retention
      iv. 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.
      v. Avoid abrupt discontinuation; can precipitate clinical deterioration
      vi. May not notice improvement in symptoms for several months
      vii. Should be considered even in patients with reactive airway disease or asymptomatic bradycardia
   d. Monitoring
      i. BP, HR, and symptoms of hypotension (monitor in 1–2 weeks)
         a) Significant hypotension, bradycardia, or dizziness occurs in about 1% of patients on β-blocker therapy when the β-blocker is titrated slowly. If these symptoms appear, lower the dose by 50%.
         b) 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 dose first.
      ii. Increased edema/fluid retention (monitor in 1–2 weeks)
         a) From 1% to 2% more common than placebo (in euvoletic, stable patients)
         b) Responds to diuretic increase
iii. Fatigue or weakness
   (a) From 1% to 2% more common than placebo
   (b) Usually resolves spontaneously in several weeks
   (c) 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/day</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg bid</td>
<td>25 mg bida</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg/day</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>Metoprolol succinate XLb</td>
<td>12.5–25 mg/day</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
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<td>f</td>
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</tbody>
</table>

5. Aldosterone receptor antagonists
   a. Place in therapy
      i. Recommended in class II–IV patients with an LVEF of 35% or less to reduce morbidity and mortality unless a contraindication exists. Patients with class II should have a history of CV hospitalization or elevated brain natriuretic peptide (BNP) levels. (class I indication)
      ii. 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 diabetes (class I indication)
   b. Benefits of spironolactone in NYHA class III and IV HF
      i. Decreased all-cause mortality (30% relative risk reduction vs. placebo)
      ii. Decreased hospitalizations for HF (35% relative risk reduction vs. placebo)
      iii. Improved symptoms
   c. Benefits of eplerenone (selective aldosterone antagonist) in NYHA class II HF
      i. Decreased death from CV causes or hospitalization from HF (37% relative risk reduction vs. placebo)
      ii. Decreased hospitalizations from HF (42% relative risk reduction vs. placebo)
      iii. Decreased mortality (24% relative risk reduction vs. placebo)
   d. Benefits of eplerenone in LV dysfunction after MI
      i. Decreased mortality (15% relative risk reduction vs. placebo)
      ii. Decreased the composite of death from CV causes or hospitalization for CV events (13% relative reduction vs. placebo)
   e. Mechanism of action: Blocks effects of aldosterone in the kidneys, heart, and vasculature
      i. Decreases K and Mg loss: Decreases ventricular arrhythmias
      ii. Decreases Na retention; decreases fluid retention
      iii. Eliminates catecholamine potentiation; decreases BP
      iv. Blocks direct fibrotic actions on the myocardium
   f. Dosing and administration considerations
      i. Should be added to ACE inhibitor (or ARB) and β-blocker therapy
      ii. SCr should be less than 2.5 mg/dL for men and less than 2.0 mg/dL in women, and K should be less than 5.0 mEq/L. Dosing:
         (a) Spironolactone 12.5–25 mg/day
         (b) Eplerenone 25–50 mg/day
         (c) Avoid use if SCr is greater than 2.5 mg/dL, creatinine clearance (CrCl) is less than 30 mL/minute, or K is greater than 5.0 mEq/L.
(d) In the absence of hypokalemia (K less than 4.0 mEq/L), supplemental K is not recommended when taking an aldosterone antagonist.

g. Monitoring
   i. K and SCr within 2–3 days and again at 7 days after starting therapy; then monthly for first 3 months; then every 3 months thereafter. If the dose of ACE inhibitor or ARB is increased, restart monitoring.
      (a) Hyperkalemia was reported in only 2% of the patients in the trial; however, in practice, it occurs in about 20% of patients.
      (b) Decrease dose by 50% or discontinue if K is greater than 5.5 mEq/L.
   ii. Gynecomastia
      (a) Spironolactone is reported at a rate of 10% in clinical trials.
      (b) Eplerenone may be considered an alternative to spironolactone in painful gynecomastia.

Table 6. Dosing of Aldosterone Antagonists

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Eplerenone</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated CrCl &gt; 50 mL/minute and K ≤ 5 mEq/L</td>
<td>25 mg once daily</td>
<td>12.5–25 mg once daily</td>
</tr>
<tr>
<td>Maintenance dose after 1 month if K ≤ 5 mEq/L and CrCl &gt; 50 mL/minute</td>
<td>50 mg once daily</td>
<td>25 mg once or twice daily</td>
</tr>
<tr>
<td>Estimated CrCl 30–40 mL/minute</td>
<td>25 mg every other day</td>
<td>12.5 mg once daily or every other day</td>
</tr>
<tr>
<td>Maintenance dose after 1 month if K ≤ 5 mEq/L and CrCl &gt; 30–49 mL/minute</td>
<td>25 mg once daily</td>
<td>12.5–25 mg once daily</td>
</tr>
</tbody>
</table>

6. Digoxin
   a. Place in therapy: Can be beneficial in decreasing hospitalizations in patients with HFrEF (class IIa indication)
   b. Benefits
      i. Improved symptoms
      ii. Improved exercise tolerance
      iii. Decreased hospitalizations
      iv. No effect on mortality
   c. Mechanism of action (in HF): Inhibits Na-K ATP
      i. Decreases central sympathetic outflow by sensitizing cardiac baroreceptors
      ii. Decreases renal reabsorption of Na
      iii. Minimal increase in cardiac contractility because of the inhibition of Na-K ATP
   d. Dosing and administration recommendations
      i. SCr should be monitored because the drug is cleared more than 95% renally.
      ii. For most patients, 0.125 mg/day is adequate to achieve the desired serum concentration.
      iii. 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.
      iv. No indication to load patients with digoxin in the setting of HF
   v. Drug interactions. Digoxin concentrations are increased with concomitant:
      (a) Clarithromycin, erythromycin
      (b) Amiodarone, dronedarone
      (c) Itraconazole, posaconazole, voriconazole
      (d) Cyclosporine, tacrolimus
      (e) Verapamil
e. Monitoring: Serum concentrations should be less than 1.0 ng/mL; in general, concentrations of 0.5–0.9 ng/mL are suggested.
   i. Minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations
   ii. Risk of toxicity increases with age and renal dysfunction.
   iii. Risk of toxicity increases in the presence of hypokalemia, hypomagnesemia, or hypercalcemia
   iv. Signs of toxicity generally include, nausea, vomiting, vision changes

7. Hydralazine/isosorbide dinitrate
   a. Place in therapy
      i. Recommended in addition to ACE inhibitors and β-blockers to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III or IV HFrEF (class I indication)
      ii. May be useful in patients with current or prior symptoms of HFrEF who are unable to tolerate an ACE inhibitor or an ARB (class IIa indication)
   b. Benefits
      i. Decreased mortality (43% relative risk vs. placebo)
      ii. Decreased hospitalizations (39% relative risk vs. placebo)
   c. Mechanism of action
      i. Hydralazine
         (a) Arterial vasodilator (reduces afterload)
         (b) Enhances effect of nitrates through antioxidant mechanisms
      ii. Isosorbide dinitrate
         (a) Stimulates nitric acid signaling in the endothelium
         (b) Effective in reducing preload
   d. Dosing and administration considerations
      i. Hydralazine (25–75 mg three or four times daily); isosorbide dinitrate (10–40 mg three times daily)
      ii. Fixed-dose BiDil (hydralazine 37.5 mg plus isosorbide dinitrate 20 mg) with a goal dose of 2 tablets three times daily
   e. Monitoring
      i. Headache
      ii. Hypotension
      iii. Drug-induced lupus with hydralazine

8. Device therapy
   a. ICD (implantable cardioverter defibrillator)
      i. Recommended for primary prevention of sudden cardiac death in ischemic and nonischemic patients
         (a) Qualifying criteria include 40 days post-MI, LVEF of 35% or less, or NYHA class II or III symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year.
         (b) Patients 40 days post-MI, LVEF of 30% or less, and NYHA class I symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year.
      ii. Chronic resynchronization therapy is recommended for those with an LVEF of 35% or less, in sinus rhythm, and a left bundle branch block with a QRS of 150 milliseconds or greater on optimal medical therapy with NYHA class II–III symptoms or NYHA class IV with ambulation.
   b. Anticoagulation
      i. Recommended in HF with permanent/persistent/paroxysmal atrial fibrillation (AF) with an additional risk factor for stroke (no preference on agent)
      ii. Reasonable in patients with HF who have permanent/persistent/paroxysmal AF without an additional risk factor for stroke
      iii. Not recommended in the absence of AF, prior stroke, or a cardioembolic source
c. Statins: Not recommended solely on the basis of HF diagnosis
d. Omega-3 fatty acids: Reasonable adjunctive therapy in NYHA class II–IV symptoms and HFrEF or HFpEF
e. Antiarrhythmics: Amiodarone and dofetilide are the only two that should be used in HFrEF for patients with arrhythmias.

C. Nonpharmacologic Therapy for HFrEF
1. Prevent further cardiac injury.
   a. Discontinue smoking.
   b. Reduce weight if obese.
   c. Control HTN.
   d. Control diabetes mellitus.
   e. Minimize alcohol to 2 or fewer drinks a day for men and 1 or fewer drinks a day for women.
   f. Eliminate alcohol if cardiomyopathy is alcohol induced.
   g. Limit Na intake to 1500 mg/day for stages A and B consider less than 3 g/day for stages C and D.
2. Restricting fluid intake to 1.5–2 L/day is reasonable in stage D if serum sodium is low.
3. Modest exercise program benefits
   a. Possible modest effects on all-cause hospitalization and all-cause mortality, CV death or CV hospitalization, and CV death or HF hospitalization
   b. Safe for patients with HF
4. Annual influenza vaccine and pneumococcal vaccine every 5 years
5. Monitor and appropriately replace electrolytes (minimize risk of arrhythmias).
   a. Hypothyroidism may be masked by HF symptoms.
   b. Hyperthyroidism will worsen systolic dysfunction.
7. Screen for and treat depression.

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

D. Drugs to Avoid or Use with Caution in HFrEF
1. Nonsteroidal anti-inflammatory drugs (NSAIDs, including selective cyclooxygenase-2 inhibitors)
   a. Promote Na and water retention
   b. Blunt diuretic response
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 proven safe in patients with HF.
   d. Avoid dronedarone. Contraindicated in patients with symptomatic HF with recent decompensation requiring hospitalization or NYHA class IV HF
4. Calcium channel blockers (CCBs) \textit{(except for amlodipine and felodipine)}
   a. Negative inotropic activity
   b. Neurohormonal activation
   c. Amlodipine and felodipine have been proven safe in patients with HF.
5. Minoxidil
   a. Fluid retention
   b. Stimulation of the renin-angiotensin-aldosterone system
6. Thiazolidinediones: Fluid retention
7. Metformin: Increased risk of lactic acidosis (black box warning)
8. Amphetamines (e.g., methylphenidate)
   a. \(\alpha\)- and \(\beta\)-agonist activity
   b. Tachycardia
   c. Atrial and ventricular arrhythmias
9. Nutritional supplements
10. Hormonal therapies
11. Cilostazol: Inhibition of phosphodiesterase type-3
12. Itraconazole: Negative inotropic activity
13. Pregabalin
   a. Inhibition of calcium channels
   b. Lower extremity edema, HF exacerbation

\textbf{Figure 1.} Algorithm for pharmacologic management of HFrEF.

\begin{itemize}
\item ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CrCl = creatinine clearance;
\item HFrEF = heart failure with preserved EF; K = potassium; NYHA = New York Heart Association.
\end{itemize}


\textit{In contrast of objective data to guide therapy for patients with diastolic dysfunction. The following recommendations are based on the large number of trials and the patients with systolic dysfunction who have been studied, there is a lack primarily on the consensus opinion of cardiovascular (CV) experts.}
**HFpEF or Diastolic Dysfunction**

E. General Treatment Goals of Diastolic Dysfunction
   1. Control HTN according to published guidelines.
      a. HTN impairs myocardial relaxation.
      b. HTN promotes cardiac hypertrophy.
   2. Control tachycardia.
      a. Tachycardia decreases the time for the ventricles and coronary arteries to fill with blood.
      b. Control of HR improves symptoms of HF.
      c. Can use β-blockers, non-dihydropyridine CCBs, and/or digoxin
   3. Reduce preload (but not too much!)
      a. Ventricular filling pressure is primarily determined by central blood volume.
      b. Patients with diastolic dysfunction are more preload-dependent for ventricular filling. Decreasing the preload too much may cause unexpected hypotension.
      c. Symptoms of breathlessness can be relieved using diuretics or nitrates.
   4. Aggressively investigate, repair, and treat myocardial ischemia.
      a. Myocardial ischemia impairs ventricular relaxation.
      b. Any ischemia possibly contributing to diastolic dysfunction warrants aggressive therapy.

F. Pharmacologic Therapy for Diastolic Dysfunction
   1. ACE inhibitors
      a. Reduction in hospitalizations
      b. Treat HTN.
   2. Angiotensin receptor blockers:
      a. Reduction in hospitalizations
      b. Treat HTN.
   3. Digoxin
      a. No effect on all-cause mortality or all-cause CV hospitalizations
      b. Possible increase in unstable angina admissions
   4. β-Blockers, verapamil, and diltiazem: Benefits are targeted symptom relief.

**Patient Case**

4. P.M. is a 52-year-old man (weight 116 kg, height 178 cm) with a history of HTN and a TIA 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. For his HTN, he takes metoprolol tartrate 50 mg twice daily and aspirin 81 mg/day. He is adherent to this regimen and has health insurance, but he does not like to make the trip to his primary care provider because it is a 3-hour drive. His laboratory data from his past visit were all within normal limits. His vital signs today include BP 130/78 mm Hg and HR 76 beats/minute. All laboratory values are within normal limits. An ECG reveals an irregularly irregular rhythm, with no P waves, and a ventricular rate of 74 beats/minute. A diagnosis of AF is made. Which is the best approach for managing his AF?
   A. Begin digoxin 0.25 mg/day.
   B. Begin diltiazem CD 240 mg/day.
   C. Begin warfarin 5 mg/day and titrate to a goal INR of 2.5.
   D. Begin dabigatran 150 mg twice daily.
II. ATRIAL FIBRILLATION

A. Background
   1. Prevalence
      a. Most common arrhythmia: 2.2 million Americans
      b. Prevalence increases with age
      c. Common comorbidity in patients with valvular heart disease or HF
   2. Symptoms
      a. Some patients have no symptoms.
      b. At worst, an embolic event may occur or symptoms of HF may be present.
      c. Potential symptoms that may be present to some degree include the following:
         i. Palpitations
         ii. Chest pain
         iii. Dyspnea
         iv. Fatigue
         v. Light-headedness
      d. Symptoms vary with ventricular rate, underlying LV functional status, AF duration, and individual patient perceptions.
   3. Classification (more than one of these may exist in a given patient):
      a. Paroxysmal—spontaneous self-termination within 7 days of onset
      b. Persistent—lasting more than 7 days
      c. Permanent—present all the time, unable to return to normal sinus rhythm using pharmacologic or nonpharmacologic options
      d. Recurrent—two or more episodes

B. Pathophysiology
   1. Cardiac conduction
Figure 2. Cardiac conduction and atrial fibrillation.

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

Figure 3. Electrocardiogram showing atrial fibrillation.

3. These abnormal impulses can occur from many causes.
Table 7. Potential Causes of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Atrial Distension</th>
<th>High Adrenergic Tone</th>
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<tbody>
<tr>
<td>Chronic hypertension</td>
<td>Alcohol withdrawal</td>
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<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>Excessive theophylline, caffeine</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>Surgery</td>
</tr>
<tr>
<td>Emphysema or other lung diseases</td>
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</table>

C. Pharmacologic Therapy

1. Ventricular rate control
   a. If patients have a rapid ventricular rate, AV node blockade is required.
   b. Goal HR is less than 110 beats/minute at rest in patients with persistent AF who have stable ventricular function (LVEF greater than 40%). For patients with an LVEF of 40% or less or AF symptoms, the HR goal is less than 80 beats/minute at rest and 100 beats/minute with exercise.
   c. Goal is to reduce symptoms and possibly prevent tachycardia-induced cardiomyopathy.
   d. Select the best agent according to individual clinical response and concomitant disease state(s).
   e. These therapies have no effect on the cardioversion of AF:
      i. β-blockers
         (a) Any agent with β-blockade can be used and dosed to the goal HR.
         (b) Selective β1-antagonists (e.g., atenolol, metoprolol) may be preferred.
         (c) Labetalol or carvedilol if additional α1-blockade is desirable (e.g., HTN)
         (d) Effective for controlling exercise-associated HR increases
         (e) Can be considered in patients with stable HF (only carvedilol, metoprolol CR/XL, or bisoprolol)
         (f) Avoid in patients with Wolff-Parkinson-White syndrome.
      ii. Non-dihydropyridine CCBs: Verapamil or diltiazem
          (a) Avoid use if there is concomitant systolic dysfunction.
          (b) May be preferred over β-blocker in patients with asthma/severe chronic obstructive pulmonary disease
          (c) Effective for controlling exercise-associated HR increases
          (d) Avoid in patients with Wolff-Parkinson-White syndrome.
      iii. Digoxin
           (a) Often ineffective alone for controlling ventricular rate in AF, especially during exercise or movement (because of minimal effectiveness with sympathetic stimulation)
           (b) Can be included in regimen if patient has systolic HF
           (c) May be effective if additional HR control is needed when a patient is receiving a β-blocker, diltiazem, or verapamil
           (d) Avoid in patients with Wolff-Parkinson-White syndrome.
      iv. Amiodarone
          (a) May be used for rate control in patients with HF who do not have an accessory pathway
          (b) May be used for rate control in patients who are refractory to other therapies such as β-blockers, non-dihydropyridine CCBs, and digoxin
2. Antithrombotic therapy
   a. The average annual stroke rate is 5% per year without anticoagulation.
      i. A patient’s individual risk may vary from about 1% to 20% per year, depending on his or her risk factors.
      ii. This risk is independent of current cardiac status (i.e., sinus rhythm or AF).
   b. Risk stratification and treatment determination

Table 8. Risk Stratification for Antithrombotic Therapy Using the CHADS\textsubscript{2} Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
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<tbody>
<tr>
<td>C</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
</tr>
<tr>
<td>A</td>
<td>Age ( \geq 75 ) years</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes</td>
</tr>
<tr>
<td>( S_2 )</td>
<td>Stroke or TIA</td>
</tr>
</tbody>
</table>

Note: For patients with mitral stenosis, prosthetic heart valves, prior thromboembolism, or persistent atrial thrombus on TEE, an INR goal of 25–3.5 or even higher may be indicated.

TIA = transient ischemic attack.

Step 2. Given the patient’s risk score, determine antithrombotic therapy.

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} Score = 0</th>
<th>CHADS\textsubscript{2} Score = 1</th>
<th>CHADS\textsubscript{2} Score ( \geq 2 )</th>
</tr>
</thead>
</table>

ACCF/AHA/HRS AF guidelines

| No therapy or aspirin 81–325 mg/day | OAC or aspirin 81–325 mg | OAC |

ACCP (CHEST) guidelines

| No therapy or aspirin 81–325 mg/day | Dabigatran 150 mg twice daily\textsuperscript{a} over VKA (INR 2–3) | Dabigatran 150 mg twice daily\textsuperscript{a} over VKA (INR 2–3) |

AHA/ASA nonvalvular AF guidelines

| No therapy or aspirin 81–325 mg/day | OAC or aspirin | OAC |

For high-risk patients not considered candidates for anticoagulation

Aspirin + clopidogrel

\textsuperscript{a}For nonvalvular AF.

Note: Neither rivaroxaban nor apixaban was FDA approved when the ACCP guidelines were developed.

ACCF = American College of Cardiology Foundation; ACCP = American College of Chest Physicians; AF = atrial fibrillation; AHA = American Heart Association; ASA = American Stroke Association; HRS = Heart Rhythm Society; INR = international normalized ratio; OAC = oral anticoagulant; TEE = transesophageal echocardiogram; TIA = transient ischemic attack; VKA = vitamin K antagonist.

c. Role of dabigatran
   i. Direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF
   ii. Dose: CrCl greater than 30 mL/minute—150 mg twice daily; CrCl 15–30 mL/minute—75 mg twice daily; CrCl less than 15 mL/minute—no dosing recommendations available; swallow capsules whole (do not break, crush, or chew)
   iii. Place in therapy: Selection of patients with AF and at least one additional risk factor for stroke who could benefit from treatment with dabigatran versus warfarin should consider individual clinical features, including the ability to adhere to twice-daily dosing, patient preferences, and cost
   iv. Stability: Once a bottle is opened, the medication should be used within 4 months to maintain appropriate potency.
   v. Converting from or to warfarin or parenteral anticoagulants (Table 9)

Table 9. Dabigatran Conversion Strategies to and from Oral and Parenteral Anticoagulants

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

<table>
<thead>
<tr>
<th>Converting from or to parenteral anticoagulants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Start dabigatran 0–2 hours before the next dose of the parenteral drug was to have been administered or when a continuously administered parenteral drug is discontinued (e.g., intravenous unfractionated heparin) For patients currently taking dabigatran, wait 12 hours (CrCl &gt; 30 mL/minute) or 24 hours (CrCl &lt; 30 mL/minute) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Converting from warfarin to dabigatran</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue warfarin and start dabigatran when the INR is below 2.0</td>
<td></td>
</tr>
</tbody>
</table>

Note: Because dabigatran can contribute to an increased INR, the INR will better reflect warfarin’s effect after dabigatran has been discontinued for at least 2 days. CrCl = creatinine clearance; d/c = discontinuing; INR = international normalized ratio.

vi. Drug interactions: Dabigatran is a substrate of P-glycoprotein.
   (a) P-glycoprotein inducers (e.g., rifampin mentioned only in package labeling) should be avoided; however, inhibitors such as ketoconazole, verapamil, dronedarone, amiodarone, quinidine, and clarithromycin do not require dose adjustments in patients with normal renal function. When using dabigatran in combination with dronedarone and ketoconazole (P-glycoprotein inhibitors) in patients with moderate renal dysfunction (CrCl 30–50 mL/minute), however, consider reducing the dabigatran dose to 75 mg twice daily.
Dabigatran should not be used in combination with dronedarone or ketoconazole in the setting of severe renal impairment (CrCl less than 30 mL/minute).

vii. Bleeding: In patients with AF at risk of stroke, both doses of dabigatran compared with warfarin (INR 2–3) have lower risks of both intracranial and extracranial bleeding in patients younger than 75 years. In those 75 years and older, intracranial bleeding risk is lower, but extracranial bleeding risk is similar to or higher with both doses of dabigatran compared with warfarin.

d. Role of rivaroxaban

i. Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF

ii. Dose: CrCl greater than 50 mL/minute—20 mg/day with evening meal; CrCl 15–50 mL/minute—15 mg/day with evening meal; CrCl less than 15 mL/minute—avoid use. It is preferred that rivaroxaban capsules not be crushed and swallowed whole. However, if patients unable to swallow whole, the 15 mg or 20 mg tablets may be crushed and mixed with applesauce and consumed immediately. For nasogastric or gastric feeding tubes, the 15 mg or 20 mg tablets may be crushed and suspended in 50 mL of water and administered down the tube.

iii. Place in therapy: Should consider individual clinical features, including the ability to adhere to regimen, patient preferences, and cost

iv. Converting from warfarin: Discontinue warfarin and initiate rivaroxaban once INR is below 3.0.

v. Converting from rivaroxaban to warfarin — discontinue rivaroxaban and initiate a parenteral anticoagulant and warfarin at the same time the next dose of rivaroxaban is due.

vi. Converting from anticoagulants other than warfarin: Administer rivaroxaban 0–2 hours before the next scheduled evening dose of current anticoagulant.

vii. Converting from unfractionated heparin (UFH) continuous infusion: Discontinue UFH and initiate rivaroxaban at the same time.

viii. Drug interactions. Rivaroxaban is a substrate of cytochrome P450 (CYP) 3A4/5 and P-glycoprotein.

(a) Combined strong CYP3A4 and P-glycoprotein inhibitors (ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, conivaptan): Avoid administration of rivaroxaban.

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

(c) Combined P-gp inhibitor and moderate CYP3A4 inhibitors (eg. amiodarone, diltiazem, dronedarone, erythromycin). Avoid use if CrCl 15 to 80 mL/min.

ix. Bleeding: No difference in the rates of major and non-major bleeding between rivaroxaban and warfarin; however, a significant reduction was seen in intracranial and fatal bleeding in the rivaroxaban group.

e. Role of apixaban

i. Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF

ii. Dose: CrCl greater than 15 mL/minute, 5 mg twice daily. In patients with at least two of the following characteristics: age 80 years or older, body weight less than 60 kg, or SCr of 1.5 mg/dL or greater: The recommended dose is 2.5 mg twice daily. For patients with end stage renal disease on maintenance hemodialysis the dose if 5 mg twice daily. A reduced dose of 2.5 mg twice daily should be used if patients are ≥ 80 years of age or ≤ 60 kg in body weight.

iii. Place in therapy: Should consider individual clinical features, including the ability to adhere to regimen, patient preferences, and cost

iv. Converting from warfarin: Discontinue warfarin and start apixaban once the INR is below 2.0. When converting to anticoagulants other than warfarin: Discontinue current anticoagulant; initiate apixaban at the time of the next scheduled dose.

v. Drug interactions: Apixaban is a substrate of CYP3A4 and P-glycoprotein.
(a) Combined strong dual CYP3A4 and P-glycoprotein inhibitors (ketoconazole, itraconazole, ritonavir, or clarithromycin): Decrease dose of apixaban to 2.5 mg twice daily or avoid concomitant use. If already taking reduced dose of apixaban, avoid use
(b) Combined strong dual inducers of CYP3A4 and P-glycoprotein (rifampin, carbamazepine, phenytoin, phenobarbital, or St. John’s wort): Avoid concomitant use.

vi. Bleeding: Major bleeding occurred in 2.13% of the apixaban-treated patients compared with 3.09% of the patients treated with warfarin (p<0.001).

f. Bleeding with warfarin
   i. Minor hemorrhage increased with therapeutic warfarin therapy
   ii. Major hemorrhage not increased with warfarin therapy at INR 2–3
   iii. Risk of intracranial hemorrhage increased with INR greater than 4

3. Rhythm control: Since the AFFIRM trial was published, it has been known that maintaining sinus rhythm offers no advantage over controlling the ventricular rate (in the typical elderly patient with AF). In fact, the rhythm control group had a higher incidence of hospitalizations, gastrointestinal (GI) adverse effects, and symptoms of HF. 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 sinus rhythm may be desirable.

Table 10. Summary of the Pros and Cons of Rate Control vs. Rhythm Control

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

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

Patient Case
5. H.D. is a 67-year-old man with a history of hypertension, 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; all laboratory results are within normal limits; however, his lower extremity edema has worsened. His INR is 2.8. His ECG shows AF. An echocardiogram shows an LVEF of 35%–40%. A rhythm control approach to H.D.’s therapy is chosen. Which is the best approach for managing his AF?
   A. Discontinue sotalol and begin metoprolol succinate 12.5 mg/day.
   B. Discontinue sotalol and begin dronedarone 400 mg twice daily.
   C. Discontinue sotalol and begin amiodarone 400 mg twice daily, tapering to goal dose of 200 mg/day for the next 6 weeks.
   D. Continue sotalol and add metoprolol tartrate 25 mg twice daily.
4. Cardioversion in AF
   a. If cardioversion is attempted (electric or pharmacologic), the absence of atrial thrombi must be ensured.
      i. Thrombi present plus cardioversion = 91% stroke rate
      ii. Without anticoagulation (caused by decreased or stagnant blood flow in the atria)
         (a) AF for greater than 48 hours = 15% rate of atrial thrombus
         (b) AF for greater than 72 hours = 30% rate of atrial thrombus
   b. Ensure safe cardioversion by either:
      i. Transesophageal echocardiogram to visualize the atria OR
      ii. Three or more weeks of therapeutic anticoagulation (INR greater than 2.0)
   c. Oral pharmacologic agents to induce/maintain sinus rhythm (choice of agent will depend on the comorbidities)
      i. Class Ic antiarrhythmics:
         (a) Flecainide and propafenone may be considered first-line therapies for patients without structural heart disease (see Figure 4).
         (b) These agents may be used second or third line because of frequent dosing requirements and adverse effect profiles; some patients require hospitalization for initiation because of proarrhythmic effects; only about 50% efficacy at 1 year
            (1) Propafenone
            (2) Flecainide
         (c) Contraindicated in patients with structural heart disease (including CAD, HF, left ventricular hypertrophy, and valvular heart disease)
      ii. Class III antiarrhythmics
         (a) Amiodarone: 85%–95% efficacy
            (1) Has electrophysiologic properties of classes I–IV
            (2) Oral loading dose required (400 mg two or three times/day × 2 weeks and then 400 mg/day for 4 weeks, followed by a 200-mg/day maintenance dose). Achieving a loading dose of 10 g is desirable. Many different regimens exist.
            (3) Long half-life of about 60 days
            (4) In addition, has AV nodal blocking properties; may help control HR if AF recurs
            (5) Useful for controlling AF associated with Wolff-Parkinson-White syndrome if class IC drugs (e.g., flecainide and propafenone) have failed or if they are contraindicated
            (6) Safe to use in patients with HF
            (7) Hepatically metabolized: CYP3A4 substrate; inhibitor of CYP3A4, CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein
            (8) Minimal incidence of ventricular arrhythmias
            (9) Drug interactions (many)
               (A) Digoxin—Increased digoxin exposure. Lower initial digoxin dose by 50%
               (B) Warfarin—Increased warfarin exposure. Lower warfarin dose by 25%–30%
               (C) Simvastatin—Increased simvastatin exposure. Do not exceed dose of 20 mg/day.
               (D) Lovastatin—Increased lovastatin exposure. Do not exceed dose of 40 mg/day.
               (E) β-Blockers—Additive bradycardia
               (F) Non-dihydropyridine CCBs—Additive bradycardia
            (10) Extensive monitoring for noncardiac adverse effects
               (A) Liver function tests (LFTs): Baseline and every 6 months
               (B) Thyroid function tests: Baseline and every 6 months
               (C) Chest radiography: Baseline and annually
               (D) Pulmonary function tests (including DLCO(2) [carbon dioxide diffusion in the lungs]): Baseline and for unexplained dyspnea or chest radiographic abnormalities. Discontinue if pulmonary fibrosis occurs.
(E) Ophthalmologic examination: For symptoms of visual impairment. Discontinue if optic neuritis occurs.

(F) Skin toxicities: “Blue skin” syndrome and sunburn

(G) Neurologic toxicity: Monitor for neuropathy.

(b) Sotalol: 50%–60% efficacy

(1) Renal excretion; hence, dose adjustment and vigilant corrected QT (QTc)-interval monitoring necessary in renal impairment

(2) Should be initiated in the hospital for a minimum of 3 days, where QTc, serum electrolytes (e.g., K and Mg), and renal function can be monitored

(3) Contraindicated in patients with HF, CrCl less than 40 mL/minute, or QTc interval greater than 440 milliseconds, sinus bradycardia, second- or third-degree AV block without functioning pacemaker

(c) Dofetilide: 50%–60% efficacy

(1) Must be initiated in the hospital (3-day stay). Dose adjusted according to renal function and QTc-interval response. Renal dosing: If 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

(2) Hepatically metabolized by CYP3A

(3) Renal elimination through renal cationic secretion; check QTc interval if renal function acutely declines

(4) Contraindicated in patients with CrCl less than 20 mL/minute or QTc interval greater than 400 milliseconds (or 500 milliseconds for patients with ventricular conduction abnormalities)

(5) Safe to use in patients with HF

(6) Drug interactions:

(A) Cimetidine, verapamil, itraconazole, ketoconazole, hydrochlorothiazide, prochlorperazine, megestrol, and trimethoprim alone or in combination with sulfamethoxazole: AVOID

(B) CYP3A4 inhibitors: Increased dofetilide exposure, so use with caution

(C) Triamterene, metformin, amiloride: Increased dofetilide exposure, use with caution

(d) Dronedarone: 21%–25% efficacy

(1) Amiodarone analog lacking the iodine moiety that contributes to the pulmonary, thyroid, hepatic, and ocular toxicity of amiodarone

(2) Has electrophysiologic properties of classes I–IV with minimal proarrhythmic effects

(3) Dose: 400 mg twice daily with morning and evening meal

(4) Hepatically metabolized; CYP3A4 substrate and moderate CYP3A4, CYP2D6, and P-glycoprotein inhibitors

(5) Half-life is 13–19 hours.

(6) Can increase SCr within 7 days (by 0.1 mg/dL—not clinically important)

(7) Contraindicated in permanent AF, NYHA class II or III HF with recent decompensation requiring hospitalization, NYHA class IV HF, severe liver impairment, HR less than 50 beats/minute, concurrent use of strong CYP3A4 inhibitors or QTc-interval–prolonging agents, history of amiodarone-induced hepatotoxicity or pulmonary toxicity, pregnancy, or QTc interval greater than 500 milliseconds

(8) One meta-analysis found dronedarone less effective than amiodarone for the maintenance of sinus rhythm, but with fewer adverse effects.

(9) Drug interactions

(A) Digoxin: Increased digoxin exposure; lower digoxin dose by 50%.
(B) Diltiazem, verapamil, β-blockers: Excessive bradycardia; initiate these drugs at lowest dose. Diltiazem and verapamil can increase dronedarone exposure, so monitor ECG.
(C) Statins with CYP3A metabolism: Increased statin exposure. Follow statin package labeling for CYP3A4 inhibitors.
(D) Dabigatran: In patients with moderate renal impairment (CrCl 30–50 mL/minute), dronedarone increases dabigatran exposure.
(E) Strong CYP3A4 inhibitors and inducers: AVOID.
(F) Cyclosporine, tacrolimus, sirolimus: Increased exposure of these agents, monitor serum concentrations closely

(10) Other safety issues:
(A) Use in permanent AF: The use of dronedarone should be avoided.
(B) Liver injury: According to postmarketing surveillance, dronedarone has been associated with rare but severe hepatic liver injury.
(C) 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.

<table>
<thead>
<tr>
<th>Table 11. Anticoagulation Strategies Surrounding Cardioversion of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unstable</strong></td>
</tr>
</tbody>
</table>
| Stable, duration < 48 hours | ACCP (CHEST) guidelines:  
• Anticoagulate at presentation and continue through cardioversion  
  – LMWH or UFH at full treatment doses  
• Anticoagulate for at least 4 weeks afterward, regardless of baseline risk of stroke  
  – ACC/AHA/HRS AF guidelines:  
  • During the first 48 hours, the need for anticoagulation before and after cardioversion may be based on the patient’s risk of thromboembolism |
| Stable, duration unknown, or > 48 hours | ACCP (CHEST) guidelines:  
• Anticoagulate for 3 weeks before cardioversion  
  – VKA with INR 2.0–3.0, LMWH at full treatment dose, or dabigatran  
ACC/AHA/HRS AF guidelines:  
• Anticoagulate for 3 weeks before cardioversion regardless of the method (electrical or pharmacologic) used to restore sinus rhythm  
  – Limited data support LMWH in this indication |
| TEE-guided cardioversion for stable, duration unknown, or > 48 hours | 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 hours of TEE if no thrombus is seen  
• Anticoagulate for 4 weeks after cardioversion regardless of baseline risk of stroke  
  • ACC/AHA/HRS AF guidelines:  
  • If no identifiable thrombus seen on TEE, cardioversion is reasonable immediately after anticoagulation with UFH bridged to VKA or dabigatran (4 weeks) |

*Potential risk of conversion with amiodarone should be considered before treatment initiation.
No randomized trials have compared different anticoagulation strategies in patients with AF < 48 hours.
ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AF = atrial fibrillation; AHA = American Heart Association; HRS = Heart Rhythm Society; INR = international normalized ratio; IV = intravenous; LMWH = low-molecular-weight heparin; TEE = transesophageal echocardiography; UFH = unfractionated heparin; VKA = vitamin K antagonist.
Figure 4. Choice of pharmacotherapy for maintenance of sinus rhythm.

CAD = coronary artery disease; LVH = left ventricular hypertrophy.


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

III. HYPERTENSION

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

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

4. Benefits of lowering BP
   a. Decreased risk of stroke (by 40%)
   b. Decreased risk of MI (by 25%)
   c. Decreased risk of HF (by 50%)

5. Effects of lifestyle modifications on BP

<table>
<thead>
<tr>
<th>Table 12. Recommended Lifestyle Modifications</th>
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<tbody>
<tr>
<td>Modification</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Weight reduction</td>
</tr>
<tr>
<td>Adopt DASH eating plan (includes substantial potassium intake)</td>
</tr>
<tr>
<td>Reduce sodium intake</td>
</tr>
<tr>
<td>Physical activity</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
</tr>
</tbody>
</table>

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

B. Therapeutic Management

1. Patient classification and management in adults: Primary classification based on systolic BP

<table>
<thead>
<tr>
<th>Table 13. Classification of BP and Hypertension and Lifestyle Modification Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP Classification</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>BP goala</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
</tr>
</tbody>
</table>

*aThis is the BP goal for most patients. Lower targets maybe needed in certain patient populations. See Table 14.*
Patient Cases

6. D.W. is a 50-year-old African American man being discharged from the hospital after an acute MI. His medical history is significant for HTN. He was taking hydrochlorothiazide 25 mg/day before hospitalization. An echocardiogram before discharge showed an LVEF of more than 60%. His vital signs include BP 150/94 mm Hg and HR 80 beats/minute. Which is the best approach for managing his HTN?
   A. Discontinue hydrochlorothiazide and add diltiazem.
   B. Continue hydrochlorothiazide and add metoprolol.
   C. Discontinue hydrochlorothiazide and add losartan.
   D. Continue hydrochlorothiazide and add losartan.

7. T.J. is a 45-year-old white woman with a history of type 2 diabetes mellitus treated with glyburide 5 mg/day. She presents to the clinic for a routine follow-up of her diabetes. Her vital signs today include BP (average of two readings) 138/88 mm Hg and HR 70 beats/minute. Her laboratory results are as follows: Na 140 mEq/L, K 4.0 mEq/L, chloride 102 mEq/L, bicarbonate 28 mEq/L, BUN 14 mg/dL, SCr 1.0 mg/dL, 24-hour urine albumin 36 mg. Of note, at her last visit, her BP was 136/85 mm Hg. Which is the best approach for managing her HTN at this time?
   A. Begin lifestyle modifications only.
   B. Begin lifestyle modifications and add amlodipine 5 mg/day.
   C. Begin lifestyle modifications and add lisinopril 2.5 mg/day.
   D. Begin lifestyle modifications and add atenolol 25 mg/day.

2. Select treatment goal.
   a. The optimal BP goal will vary depending on age, concomitant disease states, and guideline reference. Lower targets may be necessary in different patient populations such as in those with chronic kidney disease (CKD) or diabetes mellitus; African Americans; and the elderly.
   b. Several guidelines address BP goals for specific disease states. These goals are outlined in Tables 14 and 15.
### Table 14. Goal BP Values Recommended by Various Organizations

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Goal BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population age &gt; 60 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt; 150/90</td>
</tr>
<tr>
<td>General population age &lt; 60 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td>For adults age 18–80 years&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td>Patients with diabetes mellitus &gt; 18 years&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td>Patients with diabetes mellitus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt; 140/80</td>
</tr>
<tr>
<td>(Note: Lower targets [e.g., systolic BP &lt; 130 mm Hg] may be appropriate in certain individuals, such as younger patients, if target can be achieved without treatment burden)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pregnancy with diabetes</td>
<td>110–129/65–79</td>
</tr>
<tr>
<td>Patients with CKD&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td>&lt;sup&gt;a&lt;/sup&gt;For those &gt; 18 years</td>
<td></td>
</tr>
<tr>
<td>In adults both with and without diabetes having a urine albumin excretion &lt; 30 mg/24 hours (or equivalent*) whose BP is consistently &gt; 140/90 mm Hg&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td>In adults both with and without diabetes having a urine albumin excretion of ≥ 30 mg/24 hours (or equivalent*) whose BP is consistently &gt; 130/80 mm Hg systolic&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt; 130/80</td>
</tr>
<tr>
<td>Patients with HFpEF or HFrEF&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&lt; 130/80</td>
</tr>
<tr>
<td>Elderly patients&lt;sup&gt;f&lt;/sup&gt;: Age 55–79</td>
<td>SBP ≤ 140</td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>SBP 140–145</td>
</tr>
<tr>
<td>EXCEPTIONS:</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>
</tr>
<tr>
<td>(2) 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></td>
</tr>
</tbody>
</table>

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


### Table 15. Treatment Goals Based on the International Society on Hypertension in Blacks Recommendations (ISHB)\(^a\)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommended Treatment</th>
<th>Goal BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP ≥ 135/85 mm Hg without target-organ damage,(^b) preclinical CHD,(^c) or CHD(^d)</td>
<td>Lifestyle modification (&lt; 3 months without drugs) + drug therapy(^e)</td>
<td>&lt; 135/85</td>
</tr>
<tr>
<td>Secondary Prevention/Target-Organ Damage(^b,c,d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP ≥ 130/80 mm Hg with target-organ damage,(^b) preclinical CHD,(^c) or CHD(^d)</td>
<td>Lifestyle modification + drug therapy</td>
<td>&lt; 130/80</td>
</tr>
</tbody>
</table>

\(^a\) Data show that ≤ 3 months of comprehensive lifestyle modification alone should be implemented without medications if BP < 145/90 mm Hg without target-organ damage or other risk-enhancing comorbidities.

\(^b\) Target-organ damage is defined as an albumin-to-creatinine ratio greater than 200 mg/g, estimated glomerular filtration rate less than 60 mL/minute per 1.73m², or electrocardiographic or echocardiographic evidence of left ventricular hypertrophy.

\(^c\) Indicators of preclinical cardiovascular disease include metabolic syndrome, Framingham risk score greater than 20%, prediabetes (impaired fasting glucose [100–125 mg/dL] and/or impaired glucose tolerance [2-hour post-load glucose 140–199 mg/dL]), or diabetes mellitus.

\(^d\) Cardiovascular disease includes HF (systolic or diastolic), CHD/post–myocardial infarction, peripheral arterial disease, stroke, transient ischemic attack, and/or abdominal aortic aneurysm.

\(^e\) Please see the original publication for the treatment algorithm (Hypertension 2010;56:780-800).

BP = blood pressure; CHD = coronary heart disease; HF = heart failure; ISHB = International Society on Hypertension in Blacks.

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

Figure 5. AHA/ACC/CDC treatment algorithm for hypertension.


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

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


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

5. Considerations with specific antihypertensive agents
a. β-Blockers
   i. Caution with asthma or severe chronic obstructive pulmonary disease (especially higher doses) because of pulmonary β-receptor blockade
   ii. Increased risk of developing diabetes compared with an ACE inhibitor, ARB, and CCB; use caution in patients at high risk of diabetes mellitus (e.g., family history, obese)
   iii. May mask some signs of hypoglycemia in patients with diabetes mellitus
   iv. May cause depression
b. Thiazides
   i. May worsen gout by increasing serum uric acid
   ii. Increased risk of developing diabetes compared with ACE inhibitor, ARB, and CCB; use caution in patients at high risk of diabetes mellitus (e.g., family history, obese)
   iii. May assist in the management of osteoporosis by preventing urine calcium loss
c. ACE inhibitors and ARBs
   i. Contraindicated in pregnancy
   ii. Contraindicated with bilateral renal artery stenosis
   iii. Monitor K closely, especially if renal insufficiency exists or another K-sparing drug is used.
   iv. Presence of diabetic nephropathy should influence the choice of ACE inhibitor versus ARB.
d. Aliskiren  
   i. Direct renin antagonist  
   ii. Contraindicated in pregnancy  
   iii. Contraindicated in patients with diabetes when used in combination with ACE inhibitors or ARBs because of increased risk of renal impairment, hyperkalemia, and hypotension  
   iv. Avoid use in combination with cyclosporine or itraconazole.  
   v. Avoid concurrent use with ACE inhibitors or ARBs in patients with renal impairment (CrCl less than 60 mL/minute).  

6. Considerations within specific patient populations  
   a. Patients with ischemic heart disease: Potent vasodilators (hydralazine, minoxidil, and dihydropyridine CCBs) may cause reflex tachycardia, thereby increasing myocardial oxygen demand; can attenuate this by also using an AV nodal depressant (β-blocker or non-dihydropyridine CCB)  
   b. Elderly patients:  
      i. Caution with antihypertensive agents and orthostatic hypotension  
      ii. Initiate with low dose and titrate slowly.  
   c. African American patients: β-blockers and ACE inhibitors are generally less effective as monotherapy than in white patients; however, combination therapy with thiazides improves effectiveness; β-blockers and ACE inhibitors should still be used if comorbid conditions dictate  
   d. Pregnant women  
      i. Methyldopa and hydralazine are recommended if a new therapy is initiated.  
      ii. Most antihypertensives (except for ACE inhibitors, ARBs, and aliskiren) can be safely continued in pregnancy.  

7. Monitoring  
   a. Have the patient return in 4 weeks to assess efficacy.  
   b. May have patient follow up sooner if BP reading particularly worrisome  
   c. If there is an inadequate response with the first agent (and adherence is verified) and no compelling indication exists, initiate therapy with a drug from a different class.  

IV. DYSLIPIDEMIA  

A. Main Positive Risk Factors  
   1. Cigarette smoking  
   2. Hypertension (BP 140/90 mm Hg or greater or taking an antihypertensive drug)  
   3. Low HDL-C (less than 40 mg/dL)  
   4. Family history of premature CHD  
      a. CHD in male first-degree relative younger than 55 years  
      b. CHD in female first-degree relative younger than 65 years  
   5. Age (men 45 years and older; women 55 years and older)  

B. Main Negative Risk Factor: High HDL-C (greater than 60 mg/dL)  

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

D. Four Major Statin Benefit Groups
1. Individuals with ASCVD
2. Individuals with an LDL-C of 190 mg/dL or greater
3. Individuals with diabetes age 40–75 years with an LDL-C of 70–189 mg/dL and without ASCVD
4. Individuals with an LDL-C of 70–189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or greater without diabetes or ASCVD

Note: ASCVD includes CAD, stroke, and PAD.
E. RECOMMENDATIONS FOR INTENSITY OF STATIN THERAPY FOR ASCVD PREVENTION

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

Figure 7. Statin intensity recommendations for ASCVD prevention.

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.
F. High-, Moderate-, and Low-Intensity Statin Doses

Table 16. Intensity of Statin Doses

<table>
<thead>
<tr>
<th>High Intensity</th>
<th>Moderate Intensity</th>
<th>Lower Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>When taken daily, will lower LDL-C an average of ≥ 50%</td>
<td>When taken daily, will lower LDL-C an average of 30% to &lt; 50%</td>
<td>When taken daily, will lower LDL-C an average of &lt; 30%</td>
</tr>
<tr>
<td>Atorvastatin 40–80 mg</td>
<td>Atorvastatin 10–20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20–40 mg</td>
<td>Rosuvastatin 5–10 mg</td>
<td>Pravastatin 10–20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40–80 mg</td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
<td></td>
</tr>
</tbody>
</table>

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


G. Risk Assessment for Primary Prevention

1. Pooled Cohort Equation to estimate 10-year ASCVD risk
   a. Assists with identifying higher-risk individuals for statin therapy
   b. May be used in individuals with type 1 and type 2 diabetes mellitus in primary prevention to guide the intensity of statin therapy
   c. Should not be used for patients with clinical ASCVD or an LDL-C greater than 190 mg/dL already on statin therapy

2. 10-year ASCVD risk assessment is based on the Pooled Cohort Equation: http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp.
   a. Sex
   b. Age
   c. Race
   d. Total cholesterol
   e. HDL-C
   f. Systolic BP
   g. Treatment of high BP
   h. Diabetes
   i. Smoker
H. General Approach to Initiating Statin Therapy in Patients with Clinical ASCVD

- Fasting lipid panel
- ALT
- CK (if indicated)
- Evaluate for secondary causes or conditions that may affect statin safety

Evaluate and treat lab abnormalities
- LDL-C > 190 mg/dL
  - Secondary causes
  - If primary, screen for FH
- TG ≥ 500 mg/dL
- Unexplained ALT > 3 x ULN

Age ≤ 75 years without contraindications or drug-drug interactions influencing safety or history of statin intolerance
- Initiate high-intensity statin AND counsel on healthy lifestyle habits

Age > 75 years* OR with conditions influencing statin safety or history of statin intolerance
- Initiate moderate-intensity statin AND counsel on healthy lifestyle habits

Monitor therapy

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

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

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

ASCVD = atherosclerotic cardiovascular disease; CK = creatine kinase; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; ULN = upper limit of normal.

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

- **Fasting lipid panel**
- ALT
- A1C
- CK (if indicated)
- Evaluate for secondary causes or conditions that may affect statin safety

**Step 1**

- Evaluate and treat lab abnormalities
  - LDL-C > 190 mg/dL
    - Secondary causes
    - If primary, screen for FH
    - TG ≥ 500 mg/dL
    - Unexplained ALT > 3 x ULN

- Assign to statin benefit group. Counsel on healthy lifestyle habits

- Diabetes AND age 40–75 years OR LDL-C > 190 mg/dL

- No diabetes, age 40–75 years, and LDL-C 70–109 mg/dL

- Estimate 10-year ASCVD risk using Pooled Cohort Equations

  - ASCVD 10-year risk ≥ 7.5%
  - ASCVD 10-year risk 5% to less than 7.5%
  - ASCVD 10-year risk < 5%

- Patient and health care provider engage in discussion and cover
  - ASCVD risk reduction benefits
  - Adverse effects
  - Drug-drug interactions
  - Patient-specific preferences

- In select individuals, additional factors may be considered for making treatment decisions

- Initiate statin therapy. Reinforce healthy lifestyle habits

- Monitor therapy

---

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

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

ASCVD = atherosclerotic cardiovascular disease; CK = creatine kinase; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; ULN = upper limit of normal.

### Patient Cases

8. M.M. is a 63-year-old white woman who just finished 6 months of diet and exercise for dyslipidemia. She has a history of gout, chronic nonischemic HF (LVEF 26%), diet-controlled diabetes, and asthma, as well as a 15 pack-year history of tobacco (quit 3 years ago); she drinks 3 beers a day. Because she was adopted, no family history records are available. Her medications are albuterol metered dose inhaler, lisinopril, furosemide, and Tums 2 tablets/day. Her vital signs include BP 124/80 mm Hg and HR 75 beats/minute. Her laboratory results are as follows: HDL-C 64 mg/dL, LDL-C 101 mg/dL, TG 98 mg/dL, and TC 185 mg/dL. Her Pooled Cohort Equation estimates a 10-year ASCVD risk of 7.1%. Which is the most appropriate next step for M.M.?

   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. Continue lifestyle modifications and recalculate 10-year risk in 2 years.
   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.

---

J. Management 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 non-statin cholesterol-lowering agents will likely be needed.
3. Should be evaluated for genetic causes
4. Evaluate for secondary causes.

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

1. Primary goal is to prevent pancreatitis.
2. Weight loss (a 5%–10% weight loss results in a 20% reduction in TG)
3. Carbohydrates: Around 45%–50%
4. Added sugars: Less than 5%
5. Fructose: Less than 50 g
6. Protein: 20%
7. Fat – Avoid trans fats, saturated fats less than 5%, monounsaturated fats 1%–20%, polyunsaturated fats 10%–20%, EPA/DHA greater than 2 g
8. Exercise – Aerobic activity at least twice weekly
10. Pharmacologic therapy
Table 17. Common Secondary Causes of Elevated LDL-C and TG

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

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

Table 18. Effect of Lipid-Lowering Medications on Triglycerides

<table>
<thead>
<tr>
<th>Medication</th>
<th>% Decrease in Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>10–30</td>
</tr>
<tr>
<td>Fibrates</td>
<td>30–50</td>
</tr>
<tr>
<td>Immediate-release niacin</td>
<td>20–50</td>
</tr>
<tr>
<td>Extended-release niacin</td>
<td>10–30</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5–10</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>20–50</td>
</tr>
</tbody>
</table>

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

1. Efficacy
   a. Drugs of choice for high LDL-C and/or CHD or CHD risk
   b. When selecting a statin, consider the percentage of LDL-C reduction needed.
      i. \( \frac{(\text{current LDL-C} - \text{goal LDL-C})}{\text{current LDL-C}} \times 100 \)
      ii. Select an initial dose to achieve an LDL-C reduction of 30%–40%, if possible.
   c. Reduce LDL-C by 24%–60%.
   d. Reduce TG by 7%–40%.
   e. Raise HDL-C by 5%–15%.
   f. Reduce major coronary events.
   g. Reduce CHD mortality.
   h. Reduce coronary procedures (percutaneous transluminal coronary angioplasty/coronary artery bypass grafting).
      i. Reduce stroke.
      j. Reduce total mortality.
2. Mechanism of action: Inhibits enzyme responsible for converting HMG-CoA to mevalonate (rate-limiting step in production of cholesterol)
3. Main adverse effects/monitoring
   a. Myopathy (check creatine kinase [CK] at baseline and then only if muscle symptoms occur; no regular monitoring)
   b. Increased liver enzymes
      i. LFTs at baseline in all patients
      ii. Perform repeat LFTs only when clinically indicated.
      iii. Monitor for symptoms of hepatic injury.

4. Contraindications – Absolute:
   a. Active liver disease, unexplained persistent elevations in hepatic transaminases
   b. Pregnancy
   c. Nursing mothers
   d. Certain medications (agent-specific; see drug interactions below)

5. Select drug interactions (see Table 19)
   a. Fibrates: Increased risk of myopathy/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/rhabdomyolysis when used concomitantly with statins; risk is lower than with fibrates; statins and niacin are commonly used together; monitor for muscle pain.
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</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>Amlodipine</td>
<td>Daily dose not to exceed 40 mg</td>
<td>Daily dose not to exceed 20 mg</td>
<td>CI</td>
<td>Daily dose not to exceed 20 mg</td>
<td>CI with telaprevir. Daily dose not to exceed 40 mg (boceprevir)</td>
<td>CI</td>
<td>Daily dose not to exceed 5 mg</td>
</tr>
<tr>
<td>Boceprevir, telaprevir</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>Cyclosporine</td>
<td>CI</td>
<td>Daily dose not to exceed 20 mg</td>
<td>CI</td>
<td>Daily dose not to exceed 20 mg</td>
<td>CI</td>
<td>Daily dose not to exceed 5 mg</td>
<td></td>
</tr>
<tr>
<td>Danazol</td>
<td>Daily dose not to exceed 20 mg</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Daily dose not to exceed 20 mg</td>
<td>Daily dose not to exceed 10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Daily dose not to exceed 20 mg</td>
<td>Daily dose not to exceed 10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Daily dose not to exceed 20 mg</td>
<td>Daily dose not to exceed 10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin, clarithromycin, telithromycin</td>
<td>CI</td>
<td>Daily dose not to exceed 40 mg (clarithromycin)</td>
<td>CI</td>
<td>Daily dose not to exceed 1 mg (erythromycin)</td>
<td>Daily dose not to exceed 20 mg (clarithromycin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>CI</td>
<td>CI</td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Daily dose not to exceed 10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice (&gt; 1 quart per day)</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>Avoid excess quantities (&gt; 1.2 L/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole, ketoconazole, posaconazole</td>
<td>CI</td>
<td>CI</td>
<td>Daily dose not to exceed 20 mg twice daily (itraconazole)</td>
<td>Daily dose not to exceed 20 mg (itraconazole)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nefazodone</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>Niacin</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></td>
</tr>
<tr>
<td>HIV protease inhibitors</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>Ranolazine</td>
<td>Consider dose adjustment</td>
<td>Daily dose not to exceed 20 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Daily dose not to exceed 2 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
<td>CI</td>
</tr>
</tbody>
</table>

CI = contraindicated.
### Table 20. Statin Doses and LDL-C–Lowering Effect<sup>a</sup>

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>LDL-C Average Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin (Lipitor)</td>
<td>39–60</td>
</tr>
<tr>
<td>Fluvastatin (Lescol)</td>
<td>22–36</td>
</tr>
<tr>
<td>Lovastatin (Mevacor)</td>
<td>21–31</td>
</tr>
<tr>
<td>Lovastatin ER (Altocor)</td>
<td>24–41</td>
</tr>
<tr>
<td>Pitavastatin (Livalo)</td>
<td>32–43</td>
</tr>
<tr>
<td>Pravastatin (Pravachol)</td>
<td>22–37</td>
</tr>
<tr>
<td>Simvastatin (Zocor)</td>
<td>26–47</td>
</tr>
<tr>
<td>Rosuvastatin (Crestor)</td>
<td>45–63</td>
</tr>
</tbody>
</table>

<sup>a</sup>Note: For any doubling of statin dose, the LDL-C will typically decrease by only an additional 6%. LDL-C = low-density lipoprotein cholesterol.

### Table 21. Pharmacokinetic Differences Among Statins

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>Bioavailability (%)</th>
<th>Half-life (hours)</th>
<th>Elimination Metabolism</th>
<th>Prodrug</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>12</td>
<td>14</td>
<td>3A4</td>
<td>No</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>24</td>
<td>1</td>
<td>2C9</td>
<td>No</td>
<td>Hydrophilic</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>51</td>
<td>12</td>
<td>2C9, 2C8</td>
<td>Yes</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>17</td>
<td>1.5–2</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>20</td>
<td>2C19</td>
<td>No</td>
<td>Hydrophilic</td>
</tr>
</tbody>
</table>

N/A = not applicable.
Table 22. Dosing of Statin Agents in Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>eGFR (mL/minute)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30–59</td>
<td>15–29</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10–80 mg</td>
<td>10–80 mg</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>10–80 mg</td>
<td>10–40 mg</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>20–80 mg</td>
<td>10–40 mg</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>1–2 mg</td>
<td>1–2 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20–80 mg</td>
<td>10–40 mg</td>
</tr>
<tr>
<td>Simvastatina</td>
<td>20–80 mg</td>
<td>10–20 mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5–40 mg</td>
<td>5–10 mg</td>
</tr>
</tbody>
</table>

a The 80-mg dose of simvastatin should be reserved for patients who have been taking simvastatin 80 mg long term (e.g., ≥ 12 months) and who are without evidence of muscle toxicity.
b No data available; cannot recommend.
CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; HD = hemodialysis.

M. Bile Acid Sequestrants (cholestyramine, colestipol, colesevelam)

1. Efficacy
   a. Reduce LDL-C by 15%–26%.
   b. Raise HDL-C by 3%–6%.
   c. May increase TG concentrations
   d. Reduce major coronary events.
   e. Reduce CHD mortality.
2. Mechanism of action: Bind to bile acids to disrupt enterohepatic recirculation of bile acids. Liver is stimulated to convert hepatocellular cholesterol to bile acids.
3. Adverse effects: GI distress/constipation
4. Decreased absorption of other drugs: Warfarin, β-blockers, levothyroxine, and thiazides; administer drugs 1–2 hours before or 4 hours after bile acid
5. Contraindications: Dysbetalipoproteinemia, raised TG concentrations (especially greater than 400 mg/dL)

N. Niacin

1. Main actions
   a. Lowers LDL-C by 15%–26%
   b. Lowers TG by 20%–50%
   c. Raises HDL-C by 15%–26%
   d. Reduces major coronary events
   e. Lowers lipoprotein (a)
2. Mechanism of action: Inhibits mobilization of free fatty acids from peripheral adipose tissue to the liver and reduces VLDL synthesis (LDL-C and TG)
3. Adverse effects/monitoring: Flushing, hyperglycemia, hyperuricemia, upper GI distress, increased hepatic transaminases; monitor LFTs at baseline, every 6–12 weeks, and then yearly
4. Sustained release appears to be more hepatotoxic than other preparations (e.g., OTCs). Available as “Slo-Niacin” or twice-daily generic niacin OTC
5. Extended release and sustained release are less likely to cause flushing.
6. Contraindications: Liver disease, severe gout, active peptic ulcer
7. Flushing can be minimized by taking aspirin 325 mg or ibuprofen 200 mg 30–60 minutes before niacin, taking at bedtime with food, and avoiding hot beverages, spicy foods, and hot showers around the time of administration.

Table 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</td>
<td>1.5–3</td>
</tr>
<tr>
<td>Immediate release</td>
<td>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>

O. Fibrates (fenofibrate, gemfibrozil)
1. Main actions
   a. Lower LDL-C by 5%–20% (with normal TG)
   b. May raise LDL-C to 45% (with very high TG)
   c. Lower TG by 30%–55%
   d. Raise HDL-C by 18%–22%
   e. Reduce progression of coronary lesions
2. Mechanism of action: Reduces rate of lipogenesis in the liver
3. Adverse effects/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

P. Ezetimibe
1. Efficacy
   a. Lowers LDL-C by 18%–20%
   b. May raise HDL-C by 1%–5%
   c. Lowers TG by 5–10%
2. Mechanism of action: Inhibition of cholesterol absorption
3. Adverse effects: Headache, rash; no monitoring necessary, except LFTs when coadministered with statins
4. Adjunctive therapy to statin
5. No outcomes data
6. Possibly increased cancer risk, but evidence is conflicting

Patient Case
10. Which best describes a potential secondary cause of high TG?
   A. Amiodarone.
   B. Biliary obstruction.
   C. Sirolimus.
   D. Saturated fats.
Q. Omega-3-Acid Ethyl Esters (Lovaza)
   1. Efficacy
      a. Lowers TG by 26%–45%
      b. May raise LDL-C to 45% when TG concentrations are very high
      c. Raises HDL-C by 11%–14%
   2. Mechanism of action: Unknown. Possible inhibition of acyl coenzyme A:1,2 diacylglycerol acyltransferase, increased hepatic β-oxidation, or reduction in TG hepatic synthesis
   3. Adverse effects: GI (e.g., burping, taste perversion, dyspepsia); at more than 3 g/day: inhibition of platelet aggregation, bleeding
   4. Used to treat hypertriglyceridemia as an adjunct to diet in adults with TG concentrations of 500 mg/dL or greater
   5. Dose: 4 g/day as a single dose or in two divided doses

R. Icosapent Ethyl (Vascepa)
   1. Efficacy
      a. Lowers TG 33%
      b. Does not appear to raise LDL-C
   2. Mechanism of action: It is suggested that EPA (eicosapentaenoic acid), the active metabolite of icosapent ethyl, reduces hepatic VLDL-TG synthesis and/or secretion and increases TG clearance from circulating VLDL particles.
   3. Adverse effects: Arthralgia
   4. Used to treat hypertriglyceridemia (500 mg/dL or greater) as an adjunct to diet
   5. Dose: 2 g twice daily with food

S. Lomitapide (Juxtapid)
   1. Efficacy: Lowers LDL-C by about 40%
   2. Mechanism of action: A selective microsomal triglyceride protein (MTP) inhibitor
   3. Indicated for homozygous familial hypercholesterolemia (HoFH)
   4. Adverse effects – Increased LFTs, GI symptoms
   5. Available only through the REMS program
   6. Dose: 5 mg once daily

T. Mipomersen (Kynamro)
   1. Efficacy: Additional 25% reduction in LDL-C
   2. Mechanism of action: Oligonucleotide targeted to human messenger RNA (mRNA)
   3. Indicated for HoFH
   4. Adverse effects – Increased LFTs, flu-like symptoms
   5. Available only through the REMS program
   6. Dose: 200 mg subcutaneously once weekly
V. CHRONIC CORONARY HEART DISEASE AND CHRONIC STABLE ANGINA

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

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

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

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

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

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

11. L.J., a 58-year-old white man, is discharged from the hospital after an NSTEMI. His medical history is significant for HTN. He was taking hydrochlorothiazide 12.5 mg/day before hospitalization. An echocardiogram shows an LVEF greater than 60%. His vital signs include BP 130/65 mm Hg and HR 64 beats/minute, and he states that he feels great. His drug regimen consists of aspirin 81 mg/day, atenolol 50 mg/day, hydrochlorothiazide 25 mg/day, atorvastatin 80 mg/day, and sublingual nitroglycerin 0.4 mg as needed for chest pain. Which represents the best action to take in response to this discharge regimen?

A. Discontinue hydrochlorothiazide; add diltiazem extended release 240 mg/day.
B. Continue hydrochlorothiazide; add amlodipine 5 mg/day.
C. Discontinue hydrochlorothiazide; add ramipril 5 mg/day.
D. Continue hydrochlorothiazide; add vitamin E 400 international units/day.

12. L.W. is a 64-year-old woman with a significant history of CHD, having had two MIs and three stent placements in the past 10 years. Her LVEF is more than 60%. She has developed shortness of breath and chest heaviness with activity during the past several months, despite being adherent to her medications. She says she is requiring up to three doses of her sublingual nitroglycerin per day; however, she has severely curtailed her activity to avoid the discomfort. She takes aspirin 81 mg/day, simvastatin 40 mg every night, enalapril 10 mg twice daily, and metoprolol tartrate 50 mg twice daily. Her vital signs include BP 132/80 mm Hg and HR 72 beats/minute. Which regimen is best to improve her stable angina symptoms and increase her activity level?

A. Discontinue metoprolol tartrate, and begin diltiazem extended release 240 mg/day.
B. Add ranolazine 500 mg twice daily.
C. Add isosorbide mononitrate 30 mg every morning.
D. Increase metoprolol tartrate to 100 mg twice daily, and add isosorbide mononitrate 30 mg every morning.

Therapeutic Management of CHD

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

B. Lipid-Lowering Therapy (see section IV: Dyslipidemia)
1. Counsel on healthy lifestyle habits
2. Fasting lipid panel, ALT, CK, consider secondary causes of dyslipidemia, evaluate for conditions that may influence statin safety
3. If LDL-C greater than 190 mg/dL, evaluate for secondary causes; if primary, screen family for familial hypercholesterolemia
4. If TG values are 500 mg/dL or greater, ensure fasting lipid panel, screen for secondary causes, employ lifestyle modifications, consider secondary causes, and consider pharmacologic therapy.

5. High-intensity statin therapy if without contraindications, drug-drug interactions, or history of statin intolerance

C. ACE Inhibitors
1. ACE inhibitors greatly decrease CV events in patients with CHD (and no LV dysfunction) at high risk of subsequent CV events.
2. Should be considered in all patients who also have an LVEF of 40% or less, HTN, diabetes mellitus, and/or CKD
3. Consider using in lower-risk patients with a mildly reduced or normal LVEF in whom CV risk factors are well controlled and revascularization has been performed.
4. Postulated mechanisms: Plaque stabilization

D. ARBs: Recommended as an alternative to ACE inhibitors in patients who also have an LVEF of 40% or less, HTN, diabetes mellitus, and/or CKD or who are unable to tolerate an ACE inhibitor (e.g., cough or angioedema)

E. Additional Therapies for Chronic Stable Angina
1. Definition: Predictable angina symptoms with exertion
2. Goals: Reduce symptoms of ischemia, increase physical function, and improve quality of life. In general, achieved by either decreasing myocardial oxygen demand or increasing myocardial oxygen supply
3. Specific agents
   a. β-Blockers
      i. Pharmacologic effects: Decreased inotropy and HR (decrease oxygen demand)
      ii. Goal resting HR 55–60 beats/minute (less than 50 beats/minute if angina symptoms continue)
      iii. May be considered chronic therapy for all patients with coronary or other vascular disease
      iv. Goal exercise HR of no more than 75% HR associated with angina symptoms
      v. Contraindications: Severe bradycardia (HR less than 50 beats/minute), high-degree AV block (without pacemaker), sick sinus syndrome (without pacemaker)
   b. Calcium channel blockers
      i. Pharmacologic effects
         (a) Decrease coronary vascular resistance and increase coronary blood flow (increase oxygen supply)
         (b) Negative inotropy, to varying degrees; nifedipine much greater than amlodipine and felodipine (decrease oxygen demand)
         (c) Decrease HR (verapamil and diltiazem only) (decrease oxygen demand)
      ii. Place in therapy
         (a) Added to β-blocker therapy to achieve HR goals
         (b) Instead of β-blocker therapy when unacceptable adverse effects emerge or if treating Prinzmetal angina
         (c) Short-acting CCBs (nifedipine, nisoldipine) have been associated with increased CV events; should be avoided (except in slow-release formulations)
      iii. Contraindications for non-dihydropyridines: Systolic HF, severe bradycardia, high-degree AV block (without pacemaker), and sick sinus syndrome (without pacemaker)
      iv. Contraindications for dihydropyridines: LV dysfunction (except amlodipine and felodipine)
   c. Nitrates
      i. Pharmacologic effects:
         (a) Endothelium-dependent vasodilation, dilates epicardial arteries and collateral vessels (increase oxygen supply)
         (b) Decreased LV volume because of decreased preload mediated by venodilation (decrease oxygen demand)
ii. Place in therapy
   (a) A scheduled nitrate is useful in conjunction with a β-blocker or non-dihydropyridine CCB (blunt the reflex sympathetic tone with nitrate therapy).
   (b) As-needed sublingual tablets or spray nitrate is necessary to relieve effort or rest angina.
   (c) In addition, as-needed nitrates can be used before exercise to avoid ischemic episodes.
iii. Contraindications: Hypertrophic obstructive cardiomyopathy, inferior wall MI, severe aortic valve stenosis, sildenafil and vardenafil within 24 hours, tadalafil within 48 hours
d. Ranolazine
   i. Pharmacologic effects
      (a) Inhibits myocardial fatty acid oxidation, causing increased glucose oxidation
      (b) Increases “oxygen efficiency”
   ii. Place in therapy
      (a) Ideal role is unclear. Currently, as a substitute for a β-blocker if initial treatment with β-blockers results in adverse effects or if β-blockers are ineffective or contraindicated
      (b) Use in combination with β-blockers, CCBs, or nitrates when initial management with these drugs is unsuccessful.
      (c) Important points
         (1) No significant effects on HR or BP; thus, bradycardia and hypotension are not of concern
         (2) Dose-related QT prolongation
         (3) Metabolized by CYP3A
            A) Avoid in hepatic dysfunction.
            B) Avoid use with strong CYP3A inhibitors, including ketoconazole,itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir.
            C) Avoid use with CYP3A inducers such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, and carbamazepine, as well as with St. John’s wort.
            D) Limit the dose of simvastatin to 20 mg daily when administered with ranolazine.
            E) Limit the dose to 500 mg twice daily in patients receiving moderate CYP3A4 inhibitors, including diltiazem, verapamil, erythromycin, and fluconazole, and in those receiving grapefruit juice.
REFERENCES

Heart Failure


Atrial Fibrillation


Hypertension


Dyslipidemia


CHD and Chronic Stable Angina


1. **Answer: A**

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

2. **Answer: B**

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

3. **Answer: C**

Cilostazol, a phosphodiesterase type-3 inhibitor, may be associated with an increased 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; hence, no additional AV node 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 CHADS, score of 3, so anticoagulation with warfarin titrated to a goal INR of 2.5 is indicated (Answer C). However, the 2012 CHEST supplement now recommends dabigatran over warfarin. In addition, this patient may be unable to travel to his primary care provider’s office for weekly INR checks. In this case, dabigatran 150 mg twice daily (Answer D) may be the best choice because it will not warrant INR monitoring; the patient has prescription insurance; he appears to be adherent to a twice-daily medication regimen already; and he does not have renal dysfunction.

5. **Answer: C**

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

6. **Answer: B**

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

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

8. Answer: A
This patient falls into one of the four statin benefit groups and therefore should be initiated on statin therapy, making Answer D incorrect. This patient would be a candidate for moderate-intensity statin therapy because she has diabetes (Answer A), and her 10-year risk is 7.5% or less. Because she falls into one of the statin benefit groups, recalculating her risk in 2 years would not be appropriate (Answer C). Because she has a 10-year risk of 7.5% or less, she is not a candidate for a high-intensity statin (Answer B), despite having diabetes. If she did not have diabetes, her 10-year risk would be only 3%, and statin therapy could be discussed as a potential option; moreover, perhaps based on the physician and patient discussion, statin therapy could be deferred and her risk recalculated in 4–6 years.

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

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

11. Answer: C
Because the patient is post-MI, his BP goal is less than 130/80 mm Hg, which he has achieved. Therefore, no decision must be made the basis of his improved BP control. Because he is post-MI, he has a compelling indication for β-blocker therapy, which he is already receiving. He has not provided any information to indicate the need for additional antianginal therapies, so adding a CCB is not necessary (Answer A and Answer B). He is taking appropriate antiplatelet and cholesterol-lowering drugs according to the requirements for individuals with CAD. An ACE inhibitor is indicated in all patients with CAD unless a contraindication exists. Ramipril is reasonable to add to this patient’s regimen, and discontinuing hydrochlorothiazide may be desirable to minimize the occurrence of hypotension (Answer C). Vitamin E therapy is not recommended in patients
with CAD because of the lack of benefit in this patient population (Answer D).

12. Answer: D
Both β-blockers and non-dihydropyridine calcium blockers can be used to achieve HR goals in patients with stable angina. However, this patient has a compelling indication for β-blockade over calcium antagonism (post-MI), and the dose of the β-blocker can be increased. Therefore, replacing the β-blocker with a non-dihydropyridine CCB is not ideal, making Answer A incorrect. Although ranolazine could be an option, its role remains unclear. Although it can be used as monotherapy, it is typically prescribed as add-on therapy to maximally tolerated conventional therapy, which this patient is currently not receiving. This rationale makes Answer B incorrect. The only available option that incorporates increased HR control with β-blockade is Answer D, which also incorporates standing nitrate therapy. Adding a nitrate by itself (Answer C) is not advisable because of the potential for reflex tachycardia in an individual who already has a higher-than-desired HR. The addition of a nitrate (increased oxygen supply) and increased β-blockade (decreased oxygen demand) is the best option for this patient.
ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

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

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

3. **Answer: A**
This patient has diastolic dysfunction, which is a problem with ventricular relaxation. The preferred therapy is either a β-blocker or a non-dihydropyridine CCB, each of which slows the HR and permits the ventricle greater time to fill with blood. Diltiazem, a non-dihydropyridine CCB, would be appropriate to initiate in this patient. Nifedipine can cause reflex tachycardia, which potentiates diastolic dysfunction by reducing ventricular filling time; therefore, this drug should be discontinued (Answer A). Diuretics should be used cautiously because patients with diastolic dysfunction are often fluid-dependent (preload) for maximal ventricular filling. In addition, this patient has no symptoms of systemic congestion, suggesting a need for increased diuresis, making Answer B incorrect. Digoxin has no role in managing diastolic dysfunction (Answer C). Although ACE inhibitors are first-line therapy for LV systolic dysfunction, they can be considered in diastolic dysfunction if further antihypertensive therapies are needed after the HR is decreased (Answer D).

4. **Answer: D**
This patient has a CHADS₂ score of 2 (risk factors are HTN and age older than 75), making him a candidate for warfarin therapy because of his AF. This will greatly decrease his risk of stroke from about 5% per year to about 1% per year. Because his HR is less than 80 beats/minute with atenolol therapy, there is no reason to discontinue atenolol, nor is there reason to add an additional rate control drug such as digoxin (Answer B) or diltiazem (Answer A). With his PAD, atorvastatin therapy is necessary, and his BP is well controlled; therefore, increasing the lisinopril dose is not warranted, making Answer A and Answer C incorrect. To derive the beneficial antiplatelet effects for CV event prevention, aspirin 81 mg is adequate. Aspirin 325 mg is also effective but has a greater risk of bleeding with concomitant warfarin. Therefore, adding warfarin and decreasing the dose of aspirin to 81 mg/day (Answer D) is correct.

5. **Answer: A**
This patient is experiencing a rapid ventricular response with exercise/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 required to control the ventricular rate adequately. A β-blocker such as metoprolol succinate is a good choice to maintain HR during activity (Answer A). Using verapamil with digoxin in this patient could result in signs or symptoms of toxicity, given his current digoxin concentration. In addition, he is already taking a CCB, making verapamil not a good choice (Answer D). The subsequent digoxin concentration may cause symptoms of toxicity. Similarly, doubling the digoxin dose would almost double the current serum concentration to 2.2 ng/dL, which should be avoided (Answer B). Instructing
the patient to avoid activity is undesirable because physical activity should be encouraged and supported in all patients, especially in those with risk factors for CV disease (Answer C).

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

7. Answer: D
This patient has been identified as being at risk of ASCVD according to his Pooled Cohort Equation result of 14.6%. Therefore, the patient falls into one of the four benefit groups (age 40–75 years and 10-year ASCVD risk of 7.5% or greater) and thus should be initiated on statin therapy. According to the guidelines, this patient should be treated with moderate- to high-intensity statin therapy. Although simvastatin 20 mg is considered a moderate-intensity dose, adding gemfibrozil to this patient’s regimen would be inappropriate because gemfibrozil is contraindicated in combination with simvastatin; also, his TG are less than 500 mg/dL and need not be specifically targeted (Answer A). Using pravastatin 20 mg would be inappropriate because this is considered a low-intensity dose, and it would not provide the more than 30%–50% reduction in LDL-C that is recommended. In addition, fenofibrate would not be needed at this time because his TG levels are lower than 500 mg/dL (Answer B). Although rosuvastatin 5 mg is a typical starting dose of this medication, it is not a moderate- to high-intensity dose and would not be appropriate (Answer C). 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: A
This patient appears to have sufficient HR control, both at rest and with exercise, so his β-blocker therapy should be continued. Discontinuing atenolol and adding nifedipine (Answer B), which is devoid of negative chronotropic effects, would not be ideal and might even worsen his angina symptoms because of a relative tachycardia, despite the increased myocardial oxygen supply. Adding amlodipine to atenolol therapy is the best choice because it optimizes the oxygen supply, which has not yet been pharmacologically addressed (Answer A). Adding antiplatelet therapy with clopidogrel (Answer C) or increasing therapy for dyslipidemia (Answer D) would not affect his acute angina symptoms.

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

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