Learning Objectives

1. Recommend patient-specific pharmacologic therapy for the management of chronic heart failure, with an emphasis on mortality-reducing agents and their target doses.

2. Develop an evidence-based pharmacologic regimen and monitoring plan for patients with atrial fibrillation.

3. Develop an optimal pharmacologic management plan for a patient with hypertension according to practice guidelines and clinical trial evidence.

4. Identify patients who are at risk of atherosclerotic cardiovascular disease (ASCVD) according to the pooled cohort equation to estimate the 10-year ASCVD risk and determine in whom statin therapy should be initiated and the appropriate intensity of statin therapy when applicable.

5. Determine the appropriate pharmacologic therapy for patients with stable coronary heart disease.

Abbreviations in This Chapter

ACC/AHA American College of Cardiology/American Heart Association
ACCP American College of Chest Physicians
ACE Angiotensin-converting enzyme
AF Atrial fibrillation
ARA Aldosterone receptor antagonist
ARB Angiotensin II receptor blocker
ASCVD Atherosclerotic cardiovascular disease
AV Atrioventricular
BNP Brain natriuretic peptide
BP Blood pressure
CCB Calcium channel blocker
CHD Coronary heart disease
CK Creatine kinase
CKD Chronic kidney disease
CO Cardiac output
CV Cardiovascular
CYP Cytochrome P450
DASH Dietary Approaches to Stop Hypertension
DBP Diastolic blood pressure
DHA Docosahexaenoic acid
DHP Dihydropyridine
DM Diabetes mellitus
DOAC Direct oral anticoagulant
ECG Electrocardiogram
EPA Eicosapentaenoic acid
GI Gastrointestinal
HDL-C High-density lipoprotein-cholesterol
HF Heart failure
HFrEF Heart failure with reduced ejection fraction
HFrEF Heart failure with preserved ejection fraction
HFSA Heart Failure Society of America
HoFH Homozygous familial hypercholesterolemia
HR Heart rate
HRS Heart Rhythm Society
HTN Hypertension
INR International normalized ratio
K Potassium
LDL-C Low-density lipoprotein-cholesterol
LFTs Liver function tests
LVEF Left ventricular ejection fraction
MI Myocardial infarction
Na Sodium
NSAID Nonsteroidal anti-inflammatory drug
NYHA New York Heart Association
P-gp P-glycoprotein
PAD Peripheral arterial disease
PCE Pooled Cohort Equation
REMS Risk Evaluation and Mitigation Strategy
SA Sinoatrial
SBP Systolic blood pressure
SCr Serum creatinine
SR Sinus rhythm
SVR Systemic vascular resistance
TC Total cholesterol
TEE Transesophageal echocardiogram
TG Triglycerides
TIA Transient ischemic attack

Self-Assessment Questions

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

1. R.S., a 58-year-old woman with a history of hypertension (HTN), coronary heart disease (CHD), myocardial infarction (MI) 4 months ago, and dyslipidemia, presents to the clinic for a follow-up. She has no worsening signs or symptoms of dyspnea or edema compared with her baseline. An echocardiogram reveals a left ventricular ejection fraction (LVEF) of 35%. She is in New York Heart Association (NYHA) class III. Her medications include aspirin 81 mg/day, metoprolol succinate
150 mg/day, and atorvastatin 40 mg every night. Her vital signs include blood pressure (BP) 138/80 mm Hg and heart rate (HR) 58 beats/minute. Her lungs are clear, and laboratory results are within normal limits. Given her history and physical examination, what is the most appropriate modification to R.S.’s current drug therapy?
A. Continue current therapy.
B. Initiate digoxin 0.125 mg/day.
C. Initiate spironolactone 25 mg/day.
D. Initiate lisinopril 5 mg/day.

2. J.O. is a 64-year-old woman with NYHA class II nonischemic dilated cardiomyopathy (LVEF of 30%). She presents to the heart failure (HF) clinic for a follow-up. She is euvolemic. Her medications include enalapril 10 mg twice daily, furosemide 40 mg twice daily, and potassium chloride 20 mEq twice daily. Her vital signs include BP 130/88 mm Hg and HR 78 beats/minute. Her laboratory results are within normal limits. What is the best way to manage J.O.’s HF?
A. Continue current regimen.
B. Increase enalapril to 20 mg twice daily.
C. Initiate carvedilol 3.125 mg twice daily.
D. Initiate digoxin 0.125 mg/day.

3. J.M. is a 65-year-old woman with a history of HTN and poor medication adherence who presents to her primary care physician with shortness of breath and markedly decreased exercise tolerance. An echocardiogram reveals an LVEF of 65%, with diastolic dysfunction. J.M.’s medications include extended-release 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 asymptomatic atrial fibrillation (AF) for the past month. His therapy includes aspirin 325 mg/day, lansoprazole 30 mg every night, atenolol 50 mg/day, lisinopril 10 mg/day, and atorvastatin 20 mg/day. His vital signs include BP 132/72 mm Hg and HR 68 beats/minute. Which is the best therapy for B.W. at this time?
A. Add diltiazem and warfarin.
B. Add digoxin and increase lisinopril to 20 mg/day.
C. Discontinue atorvastatin and add warfarin.
D. Add warfarin and decrease aspirin to 81 mg/day.

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

6. R.P. is an 69-year-old African American man with a history of HTN and gout. His medications include allopurinol 300 mg/day, amlodipine 10 mg/day, and aspirin 81 mg/day. His vital signs include BP 145/85 mm Hg and HR 82 beats/minute. His laboratory values are normal and his 10-year ASCVD risk is 22.4%. Which is the best therapy for R.P.?
A. Add hydrochlorothiazide 25 mg/day to achieve a systolic blood pressure (SBP) goal of less than 130 mm Hg.
B. Add lisinopril 40 mg/day and titrate to achieve an SBP goal of less than 140.
C. Add atenolol 50 mg/day to achieve an SBP less than 130 mm Hg.
D. Make no changes to his current medications because his SBP is at goal.

7. J.T. is a 58-year-old man who presents to his primary care provider for the first time in 10 years. He has smoked 2 packs/day for the past 30 years and takes no medication. A fasting lipid panel shows total cholesterol (TC) 222 mg/dL, low-density lipoprotein cholesterol (LDL-C) 105 mg/dL, triglycerides (TG) 330 mg/dL, and high-density lipoprotein cholesterol (HDL-C) 51 mg/dL. His vital signs include BP 140/75 mm Hg and HR 80 beats/minute. His pooled cohort equation reveals a 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 14.6%. Which would be the best pharmacologic therapy to initiate in J.T.?
A. Initiate simvastatin 20 mg/day and gemfibrozil 600 mg twice daily.
B. Initiate rosuvastatin 2.5 mg/day.
C. Initiate pravastatin 20 mg/day and fenofibrate 160 mg/day.
D. Initiate atorvastatin 20 mg/day.

8. J.S. is a 43-year-old man with HTN who presents for an annual physical examination. His family history is significant for his father having HTN. His only medication is lisinopril 10 mg/day. His BP is 145/90 mm Hg. A fasting lipid profile shows TC 238 mg/dL, TG 95 mg/dL, LDL-C 176 mg/dL, and HDL-C 43 mg/dL. His calculated 10-year ASCVD risk according to the pooled cohort equation is 3.9%. Which best describes the next step for management in J.S.?
A. Initiate high-intensity statin therapy.
B. Do not initiate statin therapy and reevaluate risk in 1–3 years.
C. Initiate moderate-intensity statin therapy.
D. Do not initiate statin therapy and reevaluate risk in 4–6 years.

9. J.C. is a 62-year-old man (height 70 inches, weight 135 kg [1 month ago 143 kg]) with a history of diabetes mellitus (DM), chronic kidney disease, bipolar disorder, CHD, and hypertriglyceridemia that, in the past, has resulted in pancreatitis. His family history is significant for his father having CHD and hypertriglyceridemia. He is not a smoker, but admits drinking a 6-pack of beer daily. Pertinent laboratory findings include a hemoglobin A1C of 11.6% and a serum creatinine (SCr) of 2.6 mg/dL. He currently takes atorvastatin 40 mg every evening, aspirin 81 mg/day, metformin 1000 mg twice daily, olanzapine 10 mg/day, metoprolol tartrate 50 mg twice daily, and coenzymeQ10 200 mg/day. His fasting lipid profile is TC 402 mg/dL, LDL-C unable to calculate, HDL-C 48 mg/dL, and TG 1500 mg/dL. His other laboratory values are within normal limits. Which best describes potential secondary causes of elevated TG concentrations that should be considered in J.C.?
A. Obesity, poorly controlled diabetes, olanzapine, metoprolol, coenzyme Q10.
B. Alcohol consumption, poorly controlled diabetes, weight loss, β-blockers.
C. Obesity, alcohol consumption, β-blockers, olanzapine.
D. Alcohol consumption, obesity, poorly controlled diabetes, olanzapine, metoprolol.

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

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

11. A.M. and her husband have decided they are ready to have children. What is the best medication option for A.M.?
   A. No change in therapy is warranted.
   B. Discontinue ramipril and replace with labetalol.
   C. Increase chlorthalidone to 50 mg/day.
   D. Discontinue all antihypertensive therapy.

12. A 66-year-old African American man (height 70 inches, weight 91 kg) with AF and CHD (non-ST-segment elevation MI and stent placement 3 years ago) presents with palpitations. Rate control therapy, including trials of β-blockers and nondihydropyridine calcium channel blockers, has been unsuccessful in controlling his symptoms. He currently takes metoprolol succinate 50 mg/day, aspirin 81 mg/day, atorvastatin 80 mg/day, lisinopril 5 mg/day, and warfarin 4 mg/day. His laboratory results show INR 2.2, potassium 4.8 mEq/L, SCr 1.2 mg/dL. His BP is 110/70 mm Hg, and his HR is 95 beats/minute. Which is the best antiarrhythmic therapy for him?
   A. Disopyramide.
   B. Flecainide.
   C. Propafenone.
   D. Sotalol.
BPS Pharmacotherapy Specialty Examination Content Outline
This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-specific pharmacotherapy
   a. Task 1: 1–8, 10, 11, 12, 13, 14, 17
   b. Task 2: 1–3
   c. Task 3: 1–2
   d. Task 4: 1–7
   e. Task 5: 1–3
   f. Systems and patient-care problems
      i. Atrial fibrillation
      ii. Chronic CHD and chronic stable angina
      iii. Heart failure
      iv. Hypertension
      v. Dyslipidemia
2. Domain 2: Retrieval, generation, interpretation, and dissemination of knowledge in pharmacotherapy, Task 2, Knowledge Statements 1–5
3. Domain 3: System and population-based pharmacotherapy, Task 2, Knowledge Statements 4–5
I. HEART FAILURE

Patient Cases

1. L.S. is a 48-year-old woman with alcohol-induced cardiomyopathy. Her most recent LVEF is 20%; her daily activities are limited by dyspnea and fatigue (NYHA class III). Her medications include lisinopril 40 mg daily, furosemide 40 mg twice daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day. She has been stable on these doses for the past month. Her most recent laboratory results include sodium (Na) 140 mEq/L, potassium (K) 4.0 mEq/L, chloride 105 mEq/L, bicarbonate 26 mEq/L, blood urea nitrogen 12 mg/dL, SCr 0.8 mg/dL, glucose 98 mg/dL, calcium 9.0 mg/dL, phosphorus 2.8 mg/dL, magnesium 2.0 mEq/L, and digoxin 0.7 ng/mL. She weighs 69 kg, and her vital signs include BP 112/70 mm Hg and HR 68 beats/minute. She has normal breath sounds and no pedal edema. What is the best approach for maximizing the management of her HF?
   A. Increase carvedilol to 25 mg twice daily.
   B. Increase lisinopril to 80 mg/day.
   C. Increase spironolactone to 50 mg/day.
   D. Increase digoxin to 0.25 mg/day.

2. J.T. is a 62-year-old man (height 72 inches, weight 85 kg) with a history of CHD (MI 3 years ago), HTN, depression, chronic kidney disease (CKD; baseline SCr 2.8 mg/dL), PAD, osteoarthritis, hypothyroidism, and HF (LVEF of 25%). His medications include aspirin 81 mg/day, simvastatin 40 mg every night, enalapril 5 mg twice daily, metoprolol succinate 50 mg/day, furosemide 80 mg twice daily, cilostazol 100 mg twice daily, acetaminophen 650 mg four times daily, sertraline 100 mg/day, and levothyroxine 0.1 mg/day. His vital signs include BP 120/70 mm Hg and HR 72 beats/minute. Pertinent laboratory results include K 4.1 mEq/L, SCr 2.8 mg/dL, and a thyroid-stimulating hormone of 2.6 mIU/L. His HF is stable and considered NYHA class II. What is the best approach for maximizing the management of his HF?
   A. Discontinue metoprolol and begin carvedilol 12.5 mg twice daily.
   B. Increase enalapril to 10 mg twice daily.
   C. Add spironolactone 25 mg/day.
   D. Add digoxin 0.125 mg/day.

A. Background: HF is a complex clinical syndrome caused by any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
   1. Prevalence
      a. Affects 5.1 million Americans
      b. Prevalence increases with age
   2. Heart failure with reduced ejection fraction (HFrEF) or systolic dysfunction
      a. Defined as a clinical diagnosis of HF and an LVEF of 40% or less
      b. Dilated ventricle
      c. Two thirds of cases are attributable to coronary heart disease (CHD).
      d. One third of cases are attributable to nonischemic cardiomyopathy.
         i. HTN
         ii. Thyroid disease
         iii. Obesity
         iv. Stress (Takotsubo)
v. Cardiotoxins
   (a) Alcohol
   (b) Cocaine
   (c) Chemotherapeutic agents
       (1) Anthracyclines
       (2) Cyclophosphamide (high dose)
       (3) Fluorouracil
       (4) Trastuzumab/pertuzumab
       (5) Mitoxantrone

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

3. Heart failure with preserved EF (HFpEF) or diastolic dysfunction
   a. Defined as an LVEF of 50% or greater; borderline HFpEF is LVEF 41%–49%
   b. Accounts for about 50% (highly variable) of patients with HF
   c. Impaired ventricular relaxation and filling
   d. Normal wall motion
   e. Most common cause is HTN (60%–89%).

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

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

Table 1. HF Stages and Corresponding NYHA Functional Class

<table>
<thead>
<tr>
<th>ACC/AHA Stage</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At high risk of HF (uncontrolled risk factors) but without structural heart disease or symptoms of HF</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but without signs or symptoms of HF</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with prior or current symptoms of HF</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions</td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology; AHA = American Heart Association; HF = heart failure; NYHA = New York Heart Association.
6. Goals of therapy
   a. Modify or control risk factors (e.g., HTN, obesity, DM)
   b. Manage structural heart disease
   c. Reduce morbidity and mortality
   d. Prevent or minimize Na and water retention
   e. Eliminate or minimize HF symptoms
   f. Block compensatory neurohormonal activation caused by reduced cardiac output (CO)
   g. Slow progression of worsening cardiac function

B. HF rEF
   1. Pharmacologic therapy (Figure 1)
      a. Diuretics
         i. Place in therapy: Indicated in patients with evidence of fluid retention (class I indication)
         ii. Short-term benefit (days)
             (a) Decreased jugular venous distension
             (b) Decreased pulmonary congestion
             (c) Decreased peripheral edema
         iii. Intermediate-term benefits (weeks to months)
             (a) Decreased daily symptoms
             (b) Increased exercise tolerance
         iv. Long-term benefits (months to years): No benefit on mortality
         v. Mechanism of action: Inhibit reabsorption of Na in the ascending limb of the loop of Henle (loops) or in the distal tubule (thiazides)
         vi. Dosing and administration considerations (Table 2)
             (a) Should be combined with an angiotensin-converting enzyme (ACE) inhibitor, β-blocker, and aldosterone receptor antagonist (ARA)
             (b) Start with a low initial dose and then double the dose and titrate according to the patient’s weight as needed. Bioavailability differs between oral loop diuretics and must be considered when converting from one agent to another.
             (c) If a patient has fluid overload, initiate and adjust therapy to result in 0.5-1 kg of weight loss per day (may be more aggressive in the inpatient setting).
             (d) Long-term therapy should be adjusted to maintain a euvoletic state.
             (e) A loop diuretic can be combined with another diuretic class (e.g., thiazide diuretic) for synergy, if needed.
             (f) Loop diuretics are preferred because of their greater diuretic capabilities; loop diuretics also retain efficacy with decreased renal function.
         vii. Monitoring: Monitor and replace K and magnesium as needed, especially with loop diuretics (goal with cardiovascular [CV] disease is K of 4.0 mEq/L or greater and magnesium of 2.0 mEq/L or greater to minimize the risk of arrhythmias). Monitor SCr and BUN to avoid acute kidney injury with overdiureses. Also monitor HCO₃ for metabolic alkalosis with overdiuresis.
Table 2. Diuretics and Recommended Dosing\(^a\)

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

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

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

BID = twice daily.

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

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

Table 3. ACE Inhibitors and Recommended Dosing

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

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

Table 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 daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>25–50 mg daily</td>
<td>150 mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20–40 mg twice daily</td>
<td>160 mg twice daily</td>
</tr>
</tbody>
</table>

ARB = angiotensin receptor blocker.

d. β-blockers
   i. Place in therapy: Recommended in all patients with HFrEF with current or prior symptoms unless contraindicated (class I indication)
ii. Benefits (when added to an ACE inhibitor)
   (a) Decreased mortality (about 35% relative risk reduction compared with placebo)
   (b) Decreased hospitalizations (about 25% relative risk reduction compared with placebo)
   (c) Symptom improvement
   (d) Improved clinical status
   (e) Notable clinical trials: CIBIS II (bisoprolol), MERIT-HF (metoprolol succinate), COPERNICUS (carvedilol), and COMET (metoprolol succinate vs. carvedilol).

iii. Mechanism of action
   (a) Blocks the effect of norepinephrine and other sympathetic neurotransmitters on the heart and vascular system
      (1) Decreases ventricular arrhythmias (sudden cardiac death)
      (2) Decreases cardiac hypertrophy and cardiac cell death
      (3) Decreases vasoconstriction and HR
   (b) Carvedilol also provides \( \alpha_1 \)-blockade.
      (1) Further decreases SVR (afterload)
      (2) Results in greater reduction in BP than metoprolol succinate

iv. Dosing and administration considerations
   (a) Only bisoprolol, carvedilol, and metoprolol succinate are recommended in HFrEF.
   (b) Add to existing ACE inhibitor therapy (at least at a low dose) when HF symptoms are stable and patients are euvoletic.
   (c) Should not be prescribed without diuretics in patients with current or recent history of fluid retention.
   (d) Start low and increase (double) the dose every 2 weeks (or slower, if needed) to target dose. Aim to achieve target dose in 8–12 weeks (Table 5).
   (e) Avoid abrupt discontinuation; can precipitate clinical deterioration
   (f) Might not notice improvement in symptoms for several months
   (g) Should be considered even in patients with reactive airway disease or asymptomatic bradycardia

Table 5. \( \beta \)-Blockers and Recommended Dosing

<table>
<thead>
<tr>
<th>Agent</th>
<th>Starting Dosage</th>
<th>Target Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25 mg twice daily</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg daily</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>Metoprolol succinate(^a)</td>
<td>12.5–25 mg daily</td>
<td>200 mg daily</td>
</tr>
</tbody>
</table>

\(^a\)50 mg twice daily if weight > 85 kg.
\(^a\)Few or no data exist for metoprolol tartrate.

CR = controlled release

v. Monitoring
   (a) BP, HR, and symptoms of hypotension or bradycardia (monitor in 1–2 weeks)
      (1) Significant hypotension, bradycardia, or dizziness occurs in about 1% of patients when the \( \beta \)-blocker is titrated slowly. If these symptoms appear, lower the dose by 50%.
      (2) Of importance, remember that higher \( \beta \)-blocker doses are associated with greater mortality reduction. Therefore, if hypotension alone is the problem, try reducing the ACE inhibitor (or another antihypertensive) first or scheduling one agent at bedtime and one in the morning.
(b) Increased edema or fluid retention (monitor in 1–2 weeks)
   (1) One percent to 2% more common than with placebo (in euvoletic, stable patients)
   (2) Responds to diuretic increase
   (3) Do not increase β-blocker dose if patient develops fluid retention during therapy initiation or titration
(c) Fatigue or weakness
   (1) One percent to 2% more common than with placebo
   (2) Usually resolves spontaneously in several weeks
   (3) May require dosage decrease or discontinuation

e. Aldosterone receptor antagonists
i. Place in therapy
   (a) Recommended in patients with NYHA class II–IV with an LVEF of 35% or less to reduce morbidity and mortality unless a contraindication exists. Patients with NYHA class II should have a history of CV hospitalization or elevated brain natriuretic peptide (BNP) levels (class I indication).
   (b) Recommended to reduce morbidity and mortality in patients after a myocardial infarction (MI) when they have an LVEF less than or equal to 40% with symptoms of HF or an LVEF less than 40% and DM (class I indication).
   (c) Benefits of spironolactone in NYHA class III and IV HF (RALES trial)
      (a) Decreased mortality (30% relative risk reduction compared with placebo)
      (b) Decreased hospitalizations for HF (35% relative risk reduction compared with placebo)
      (c) Improved symptoms
   (d) Benefits of eplerenone (selective ARA) in NYHA class II HF (EMPHASIS-HF)
      (a) Decreased composite endpoint of death from CV causes or hospitalization from HF (37% relative risk reduction compared with placebo)
      (b) Decreased death from CV causes (24% relative risk reduction compared with placebo)
      (c) Decreased hospitalizations for HF (42% relative risk reduction compared with placebo)
      (d) Decreased mortality (24% relative risk reduction compared with placebo)
   (e) Benefits of eplerenone in left ventricular dysfunction after MI (EPHESUS)
      (a) Decreased mortality (15% relative risk reduction compared with placebo)
      (b) Decreased composite endpoint of death from CV causes or hospitalization for CV events (13% relative reduction compared with placebo)

v. Mechanism of action
   (a) Blocks effects of aldosterone in the kidneys, heart, and vasculature
   (b) Decreases K and magnesium loss; decreases ventricular arrhythmias
   (c) Decreases Na retention; decreases fluid retention
   (d) Eliminates catecholamine potentiation; decreases BP
   (e) Blocks direct fibrotic actions on the myocardium

vi. Dosing and administration considerations
   (a) Should be added to ACE inhibitor (or ARB) and β-blocker therapy
   (b) SCr should be less than 2.5 mg/dL for men and less than 2.0 mg/dL in women (or estimated glomerular filtration rate greater than 30 mL/minute/1.73 m²), and K should be less than or equal to 5.0 mEq/L (Table 6).
   (c) In the absence of hypokalemia (K less than 4.0 mEq/L), supplemental K is not recommended when taking an ARA
Table 6. ARAs and Recommended Dosing

<table>
<thead>
<tr>
<th></th>
<th>eGFR ≥ 50 mL/min/1.73 m²</th>
<th>eGFR 30-49 mL/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial dose</td>
<td>Maintenance dose</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg daily</td>
<td>50 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5–25 mg daily</td>
<td>25 mg daily or BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARA = aldosterone receptor antagonist; BID = twice daily; eGFR = estimated glomerular filtration rate

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

f. Digoxin
i. Place in therapy: Can be beneficial in decreasing hospitalizations in patients with HFrEF (class IIa indication); should be added after ACE inhibitor (or ARB) and β-blocker therapy
ii. Benefits
   (a) Improved symptoms
   (b) Improved exercise tolerance
   (c) Decreased hospitalizations (28% relative risk reduction compared with placebo)
   (d) No effect on mortality
   (e) Notable clinical trial: DIG
iii. Mechanism of action (in HF)
   (a) Inhibits myocardial Na-K adenosine triphosphatase
   (b) Decreases central sympathetic outflow by sensitizing cardiac baroreceptors
   (c) Decreases renal reabsorption of Na
   (d) Minimal increase in cardiac contractility
iv. Dosing and administration considerations
   (a) For most patients, 0.125 mg/day is adequate to achieve the desired serum concentration.
   (b) Consider dosing 0.125 mg every other day in patients older than 70 years, those with impaired renal function, or those with low lean body mass.
   (c) No indication to load patients with digoxin in the setting of HF
   (d) Avoid abrupt discontinuation; can precipitate clinical deterioration
   (e) Drug interactions: Digoxin concentrations are increased with concomitant:
      (1) Clarithromycin, erythromycin
      (2) Amiodarone (reduce digoxin dose by 30%–50% or reduce dosing frequency)
      (3) Dronedarone (reduce digoxin dose by 50%)
      (4) Itraconazole, posaconazole
      (5) Cyclosporine, tacrolimus
      (6) Verapamil
v. Monitoring
(a) Serum concentrations should be less than 1 ng/mL; in general, concentrations of 0.5–0.9 ng/mL are suggested.
   (1) Minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations.
   (2) Risk of toxicity increases with age and renal impairment.
   (3) Risk of toxicity increases in the presence of hypokalemia, hypomagnesemia, or hypercalcemia.
   (4) Signs of toxicity generally include nausea, vomiting, vision changes.
(b) SCr should be monitored because the drug is primarily cleared renally.

g. Hydralazine/isosorbide dinitrate
i. Place in therapy
(a) Recommended in addition to ACE inhibitors and β-blockers to reduce morbidity and mortality for patients self-described as African American with NYHA class III or IV HF (class I indication)
(b) May be useful in patients with current or prior symptoms of HF who are unable to tolerate an ACE inhibitor or an ARB (class IIa indication)

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

iii. Mechanism of action
(a) Hydralazine
   (1) Arterial vasodilator (reduces afterload)
   (2) Increases effect of nitrates through antioxidant mechanisms
(b) Isosorbide dinitrate
   (1) Stimulates nitric acid signaling in the endothelium
   (2) Venous vasodilator (reduces preload)

iv. Dosing and administration considerations
(a) Fixed-dose BiDil (hydralazine 37.5 mg plus isosorbide dinitrate 20 mg) starting at 1 tablet three times daily with a goal dose of 2 tablets three times daily
(b) Hydralazine 75 to 300 mg daily in 3 or 4 divided doses; isosorbide dinitrate 60–120 mg daily in 3 or 4 divided doses

v. Monitoring
(a) Headache
(b) Hypotension
(c) Drug-induced lupus (with hydralazine)

h. Sacubitril/valsartan
i. Place in therapy
(a) Novel therapy approved by the U.S. Food and Drug Administration (FDA) in 2015
(b) According to the 2017 ACC/AHA/Heart Failure Society of America Focused Update of the HF guidelines
   (1) The clinical strategy of inhibition of the renin-angiotensin-aldosterone system with ACE inhibitors (level of evidence: A) OR ARBs (level of evidence: A), OR sacubitril/valsartan (level of evidence: B) in conjunction with evidence-based β-blockers and ARAs is recommended for patients with chronic HFpEF to reduce morbidity and mortality (class I recommendation)
(2) In patients with chronic symptomatic NYHA class II or III HFrEF who can tolerate an ACE inhibitor or ARB, replacement by sacubitril/valsartan is recommended to further reduce morbidity and mortality (class I recommendation).

ii. Benefits
(a) Decreased composite endpoint of death from CV causes or hospitalization for HF (20% relative risk reduction compared with enalapril monotherapy)
(b) Decreased all-cause mortality (16% relative risk reduction) and CV death (20% relative risk reduction) compared with enalapril monotherapy
(c) Decreased hospitalization for HF (21% relative risk reduction compared with enalapril monotherapy)
(d) Notable clinical trial: PARADIGM-HF

iii. Mechanism of action
(a) Sacubitril—prodrug metabolized to an active metabolite that inhibits neprilysin, increasing levels of natriuretic peptides
(b) Valsartan—ARB, selectively blocks the angiotensin I receptor and inhibits angiotensin II–dependent aldosterone release

iv. Dosing and administration considerations
(a) Initial dose
(1) Not currently taking ACE inhibitor or ARB, switching from low dose ACE inhibitor (e.g., total daily dose of enalapril ≤10 mg, lisinopril ≤ 10 mg, ramipril ≤5 mg, or equivalent) or ARB (e.g., total daily dose of valsartan ≤160 mg, losartan ≤50 mg, olmesartan ≤10 mg, or equivalent), or eGFR <30 mL/min/m²: sacubitril 24 mg/valsartan 26 mg twice daily
(2) Switching from a standard dose ACE inhibitor (e.g., total daily dose of enalapril >10 mg, lisinopril >10 mg, ramipril >5 mg, or equivalent) or ARB (e.g., total daily dose of valsartan >160 mg, losartan >50 mg, olmesartan >10 mg, or equivalent): sacubitril 49 mg/valsartan 51 mg twice daily
(b) Maintenance dose: Double the dose every 2–4 weeks to a target dose of sacubitril 97 mg/valsartan 103 mg twice daily, as tolerated.
(c) If switching from an ACE inhibitor, allow a 36-hour washout period before initiating sacubitril/valsartan.
(d) Because sacubitril is a neprilysin inhibitor, BNP will increase with use. However, NT-proBNP levels will not change.

v. Monitoring
(a) Observe for signs and symptoms of angioedema and hypotension.
(b) Monitor renal function and K 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (e.g., preexisting hypotension, DM, K supplements, azotemia).

i. Ivabradine
i. Place in therapy
(a) Novel therapy approved by the FDA in 2015
(b) According to the 2017 ACC/AHA/Heart Failure Society of America Focused Update of the HF guidelines, ivabradine can be beneficial to reduce HF hospitalizations for patients with symptomatic (NYHA class II and III), stable, chronic HFrEF (LVEF of 35% or less) who are receiving evidence-based therapies, including a β-blocker at maximum tolerated dose, and who are in sinus rhythm (SR) with an HR of 70 beats/minute or greater at rest (class IIa recommendation).
ii. Benefits
   (a) Decreased composite endpoint of CV death or hospitalization for HF (18% relative risk reduction compared with placebo)
   (b) Decreased hospitalization for HF (26% relative risk reduction compared with placebo)
   (c) Notable clinical trial: SHIFT

iii. Mechanism of action: Selectively inhibits the \( I_f \) current in the sinoatrial node, providing HR reduction

iv. Dosing and administration considerations
   (a) Given the well-proven mortality benefits of β-blocker therapy, patients should be receiving β-blockers at maximally tolerated or target doses or have a contraindication to β-blocker therapy before assessing the resting HR for consideration of ivabradine initiation.
   (b) Initial dosing: 5 mg twice daily
   (c) After 2 weeks, adjust dose according to HR:
      (1) Resting HR greater than 60 beats/minute: Increase dose by 2.5 mg twice daily.
      (2) Resting HR 50–60 beats/minute: Continue current dose.
      (3) Resting HR less than 50 beats/minute or signs/symptoms of bradycardia: Decrease dose by 2.5 mg twice daily.
   (d) Maximum dose: 7.5 mg twice daily
   (e) Contraindications: ADHF, BP <90/50 mm Hg, resting HR <60 beats/min, sinoatrial block, concomitant use with strong CYP3A4 inhibitors

v. Monitoring
   (a) Assess HR and rhythm for bradycardia (6%–10%) and AF (5%–8%) after 2 weeks of therapy initiation or modification and periodically thereafter
   (b) Phosphenes (3%): transient rings or spots of light in the visual field

j. Other medication therapies
i. Anticoagulation
   (a) Recommended for HF with permanent, persistent, or paroxysmal AF with an additional risk factor for stroke (no preference on agent)
   (b) Reasonable for patients with HF who have permanent, persistent, or paroxysmal AF without an additional risk factor for stroke
   (c) Not recommended in the absence of AF, prior stroke, or a cardioembolic source

ii. Statins: Not recommended solely on the basis of HF diagnosis

iii. Antiarrhythmics: Given the neutral effects on mortality, the preferred antiarrhythmics in patients with HFrEF are dofetilide (AF/atrial flutter) and amiodarone.

iv. Nondihydropyridine (DHP) calcium channel blockers (CCBs) with negative inotropic effects can be harmful in patients with a low EF and should be avoided (class III recommendation: harm).

v. DHP CCBs: DHP CCBs have no proven benefit on morbidity or mortality in HF. Use of amlodipine can be considered for HTN or ischemic heart disease management in HF patients because of its neutral effects on morbidity and mortality.

k. Device therapy
i. Implantable cardioverter defibrillator recommended for primary prevention of sudden cardiac death in the following patients with ischemic or nonischemic HFrEF:
   (a) Patients with ischemic or nonischemic HFrEF (LVEF of 35% of less) and NYHA class II or III symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year, and patient must be at least 40 days post-MI (class I indication).
   (b) Patients with HFrEF (LVEF of 30% or less) resulting from previous MI and NYHA class I symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year, and patient should be at least 40 days post-MI (class I indication).
Figure 1. Algorithm for pharmacologic management of heart failure with reduced ejection fraction.

*In PARADIGM-HF, patients were stabilized on an ACE inhibitor prior to conversion to sacubitril/valsartan

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


ii. Chronic resynchronization therapy recommended for those with an LVEF of 35% or less, in SR, and a left bundle branch block with a QRS of 150 milliseconds or greater on optimal medical therapy with NYHA class II–III symptoms or NYHA class IV with ambulation

2. Nonpharmacologic therapy
   a. Prevent further cardiac injury.
      i. Discontinue smoking.
      ii. Reduce weight if obese.
      iii. Control HTN (goal BP < 130/80 mm Hg per the 2017 ACC/AHA/Heart Failure Society of America Focused Update of the HF guidelines)
   iv. Control DM.
   v. Decrease alcohol intake to 2 or fewer drinks per day for men and 1 or fewer drinks per day for women. Eliminate alcohol intake if cardiomyopathy is alcohol induced.
   vi. Limit Na intake to 1500 mg/day for stages A and B; consider less than 3 g/day for stages C and D.
   vii. Treat sleep apnea.
   viii. Educate patient about appropriate self-care.
b. Restricting fluid intake to 1.5–2 L/day is reasonable in stage D if serum Na is low.
c. Modest exercise program benefits
   i. Possible modest effects on all-cause hospitalization and all-cause mortality, CV death or CV hospitalization, and CV death or HF hospitalization
   ii. Safe for patients with HF
d. Influenza and pneumococcal vaccines
e. Monitor and appropriately replace electrolytes (to minimize risk of arrhythmias).
f. Monitor for thyroid disease.
   i. Hypothyroidism can be masked by HF symptoms.
   ii. Hyperthyroidism will worsen systolic dysfunction.
g. Screen for and treat depression.

Patient Case
3. Which drug that J.T. (from Patient Case 2) is currently taking would be best to discontinue because of his HF rEF?
   A. Acetaminophen.
   B. Sertraline.
   C. Cilostazol.
   D. Levothyroxine.

C. HFpEF: Clinical evidence for efficacious agents for HFpEF has generally been disappointing. Therapies for symptoms, comorbidities, and risk factors that can worsen CV disease are recommended.
   1. Class I recommendations
      a. SBP and diastolic blood pressure (DBP) should be well controlled. HTN impairs myocardial relaxation and promotes cardiac hypertrophy. Goal SBP less than 130 mm Hg per the 2017 ACC/AHA/HFSA Focused Update of the HF guidelines
      b. Diuretics should be used for symptom relief in volume overload.
   2. Class IIa recommendations
      a. Coronary revascularization is reasonable in patients with CHD who have angina or demonstrable myocardial ischemia that is judged to be symptomatic despite optimal therapy.
      b. Management of AF is reasonable to improve symptomatic HF.
      c. The use of β-blockers, ACE inhibitors, and ARBs in patients with HTN is reasonable to control BP.
   3. Class IIb recommendation: Use of ARAs might be considered to decrease hospitalizations in patients with HFrEF already on ACE inhibitors/ARBs and β-blockers.
   4. Other recommendations
      a. Control tachycardia.
         i. Tachycardia decreases the time for the ventricles and coronary arteries to fill with blood.
         ii. Control of HR improves symptoms of HF.
         iii. Can use β-blockers or non-DHP CCBs
      b. Symptoms of breathlessness can be relieved using nitrates in addition to diuretics.
II. ATRIAL FIBRILLATION

A. Background

1. Prevalence
   a. Most common arrhythmia: 2.2 million Americans
   b. Prevalence increases with age.
   c. Common comorbidity in patients with valvular heart disease or HF

2. Symptoms
   a. Some patients have no symptoms.
   b. Potential symptoms that may be present to some degree include the following:
      i. Palpitations
      ii. Chest pain
      iii. Dyspnea
      iv. Fatigue
      v. Lightheadedness
   c. Rare cases of thromboembolic events
   d. Symptoms vary with ventricular rate, underlying LVEF, AF duration, and individual patient perceptions.

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

Patient Case

4. P.M. is a 52-year-old man (height 70 inches, weight 116 kg) with a history of HTN and a transient ischemic attack 2 years ago. He visits his primary care doctor with the chief concern of several weeks of a “fluttering” feeling in his chest on occasion. He thinks the fluttering is nothing; however, his wife insists he have it checked. His current medications include metoprolol tartrate 50 mg twice daily and aspirin 81 mg/day. He is adherent to this regimen and has health insurance, but he does not like to make the 3-hour trip to his primary care provider. His laboratory data from his past visit were all within normal limits. His vital signs today include BP 130/78 mm Hg and HR 76 beats/minute. All laboratory values are within normal limits. An electrocardiogram (ECG) reveals an irregularly irregular rhythm, with no P waves, and a HR of 74 beats/minute. A diagnosis of AF is made. What is the best approach for managing his AF at this time?

A. Begin digoxin 0.25 mg/day.
B. Begin diltiazem CD 240 mg/day.
C. Begin warfarin 5 mg/day and titrate to a goal INR of 2.5.
D. Begin dabigatran 150 mg twice daily.
B. Pathophysiology
   1. Cardiac conduction in a normal heart (this page) and a heart with atrial fibrillation (next page) (Figure 2)

   ![Cardiac conduction diagram]

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

   **Figure 2.** Cardiac conduction and atrial fibrillation.
   AV = atrioventricular; SA = sinoatrial.

   ![Reentrant pathways diagram]

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

   **Figure 2.** Cardiac conduction and atrial fibrillation. *(Cont’d)*
   AV = atrioventricular; SA = sinoatrial.

   2. ECG findings

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

**Table 7. Potential Causes of AF**

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

C. Pharmacologic therapy

1. Ventricular rate control
   a. If patients have a rapid ventricular rate, AV nodal blockade is necessary.
   b. Goal HR (resting HR less than 80 beats/minute) is reasonable in symptomatic patients (class IIa recommendation). A more lenient rate control (resting HR less than 110 beats/minute) may be reasonable in patients who are asymptomatic and have preserved ejection fraction (class IIb recommendation).
   c. The goal is to reduce symptoms and possibly prevent tachycardia-induced cardiomyopathy.
   d. Select the best agent according to individual clinical response and concomitant disease states.
      i. β-Blockers
         (a) Any agent with β-blockade can be used and dosed to the goal HR.
         (b) Labetalol or carvedilol if additional α₁-blockade is desirable (e.g., HTN)
         (c) Effective for controlling exercise-associated HR increases
         (d) Select carvedilol, metoprolol succinate, or bisoprolol in patients with HFrEF
         (e) Avoid in patients with Wolff-Parkinson-White syndrome.
      ii. Non-DHP CCBs: Verapamil or diltiazem
          (a) Avoid use if there is concomitant systolic dysfunction.
          (b) May be preferred over β-blocker in patients with asthma or severe chronic obstructive pulmonary disease
          (c) Effective for controlling exercise-associated HR increases
          (d) Avoid in patients with Wolff-Parkinson-White syndrome.
      iii. Diogxin
          (a) Often ineffective alone for controlling ventricular rate in AF, especially during exercise or movement (because of minimal effectiveness with sympathetic stimulation)
          (b) Can be included in regimen if patient has HFrEF
          (c) May be effective if additional HR control is needed when a patient is already receiving a β-blocker, diltiazem, or verapamil
          (d) Avoid in patients with Wolff-Parkinson-White syndrome.
          (e) May be agent of choice if patient has uncontrolled HR and decompensated HF
iv. Amiodarone
(a) May be used for rate control in patients with HF who do not have an accessory pathway
(b) May be used for rate control in patients who are refractory to other therapies such as β-blockers, non-DHP CCBs, and digoxin

2. Rhythm control: Maintaining SR offers no advantage over controlling the ventricular rate (AFFIRM trial). However, in specific patients with intractable and intolerable symptoms (dyspnea, palpitations, and exercise intolerance) despite adequate rate control or in patients for whom adequate ventricular rate control cannot be achieved, restoration and maintenance of SR may be desirable (Table 8).

| Table 8. Summary of the Pros and Cons of Rate Control vs. Rhythm Control |
|---|---|---|
| **Rate control strategy** | **Pros** | **Cons** |
| | Generally easy to achieve and maintain; out-of-hospital therapy typical | Electrical and structural remodeling because of continued AF makes future attainment of SR virtually impossible; safety not proven for younger patients |
| **Rhythm control strategy** | If patient is symptomatic with fatigue and exercise intolerance, these symptoms may improve if SR is attained (especially in patients with HF); minimizes development of structural atrial changes; acceptable for all age groups | Adverse effects of antiarrhythmic medications; cost of medications and monitoring; likelihood of AF recurrence; in-hospital stay may be necessary to initiate therapy |

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

a. Cardioversion in AF
i. If cardioversion is attempted (electric or pharmacologic), the absence of atrial thrombi must be ensured.
ii. Without anticoagulation (thrombi caused by decreased or stagnant blood flow in the atria)
   (a) AF for more than 48 hours = 15% rate of atrial thrombus.
   (b) AF for more than 72 hours = 30% rate of atrial thrombus.
iii. Thrombi present plus cardioversion = 91% stroke rate.
iv. Ensure safe cardioversion by either:
   (a) Transesophageal echocardiogram (TEE) to visualize the atria, or
   (b) Three or more weeks of therapeutic anticoagulation
       (1) INR 2.0-3.0 if warfarin is selected
       (2) DOACs may also be used
v. Continue anticoagulation for at least four weeks after cardioversion with either:
   (a) Warfarin or
   (b) A DOAC
vi. Specific recommendations for anticoagulation are described in Table 9.
Table 9. Anticoagulation Strategies Surrounding Cardioversion of AF∗

<table>
<thead>
<tr>
<th>AF Type</th>
<th>Anticoagulation Recommendations</th>
</tr>
</thead>
</table>
| Unstable AF                          | • Synchronized cardioversion; anticoagulate immediately beforehand with parenteral therapy  
• Anticoagulate for ≥4 wk after cardioversion with warfarin or a DOAC if AF ≥ 48 hr or if duration is unknown                                               |
| Stable AF, duration <48 hr           | ACCP (CHEST) guidelines:  
• Anticoagulate at presentation and continue through cardioversion  
  – LMWH or UFH at full treatment doses  
• Anticoagulate for ≥4 wk afterward, regardless of baseline risk of stroke                                                                               |
|                                       | ACC/AHA/HRS AF guidelines:  
• Anticoagulation as soon as possible before cardioversion is recommended with a CHA₂DS₂-VASc score of ≥2 (men) or ≥3 (women); anticoagulation may be considered with a score of 0-1 (men) or 1-2 (women)  
  – UFH, LMWH, or DOAC  
• Need for anticoagulation after cardioversion should be based on the patient’s risk of thromboembolism, according to their CHA₂DS₂-VASc score |
| Stable AF, duration unknown or >48 hr (no TEE) | ACCP (CHEST) guidelines:  
• Anticoagulate for 3 wk before cardioversion  
  – Warfarin with INR 2.0–3.0 or a DOAC  
• Anticoagulate for ≥4 wk afterward, regardless of baseline risk of stroke                                                                               |
|                                       | ACC/AHA/HRS AF guidelines:  
• Anticoagulate for ≥3 wk before cardioversion  
  – Warfarin with INR 2.0–3.0 2.0-3.0 or DOAC, dabigatran, rivaroxaban, apixaban, or enoxaparin (full treatment doses)  
• Anticoagulate for 4 wk after cardioversion, regardless of CHA₂DS₂-VASc score                                                                     |
| Stable AF, duration unknown or >48 hr (with TEE-guided cardioversion) | ACCP (CHEST) guidelines:  
• TEE-guided therapy with abbreviated anticoagulation before cardioversion  
  – LMWH or UFH at full treatment doses should be initiated at the time of TEE, and cardioversion should be performed within 24 hr of TEE if no thrombus is seen  
• Anticoagulate for ≥4 wk after cardioversion, regardless of baseline risk of stroke                                                                               |
|                                       | ACC/AHA/HRS AF guidelines:  
• If no identifiable thrombus seen on TEE, cardioversion is reasonable, provided anticoagulation is achieved before TEE  
• If thrombus identified on TEE, 3 wk of therapeutic anticoagulation is required before cardioversion  
• Anticoagulation should be maintained after cardioversion for ≥4 wk                                                                                         |

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

†No randomized trials have compared different anticoagulation strategies in patients with AF < 48 hr.

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

b. Oral antiarrhythmic agents to induce or maintain SR (choice of agent depends on patient comorbidities)
   i. Class Ic antiarrhythmics: 80% - 90% efficacy
      (a) Flecainide and propafenone can be considered first-line therapies for patients without structural heart disease (Figure 4). Propafenone also displays some nonselective β-blocking properties.
      (b) Concomitant AV nodal blocking agent (e.g., β-blocker or non-DHP CCB) typically required
      (c) Contraindicated in patients with structural heart disease (including CHD, HF, left ventricular hypertrophy, and valvular heart disease)
   ii. Class III antiarrhythmics
      (a) Amiodarone: 85%–95% efficacy
         (1) Has electrophysiologic properties of classes I–IV
         (2) Oral loading dose required (e.g., 400 mg 2 or 3 times per day for 2 weeks and then 400 mg/day for 4 weeks, followed by a 200-mg/day maintenance dose). Achieving a loading dose of 10 g is desirable. Many different regimens exist.
         (3) Long half-life of about 60 days
         (4) In addition, has AV nodal blocking properties, which may help to control HR if AF recurs
         (5) May use in patients with HF
         (6) Hepatically metabolized: Cytochrome P450 (CYP) 3A4 substrate; inhibitor of CYP3A4, CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein (P-gp)
         (7) Minimal incidence of ventricular arrhythmias
         (8) Drug interactions (many)
            (A) Digoxin: Increased digoxin exposure. Lower digoxin dose by 50%.
            (B) Warfarin: Increased warfarin exposure. Lower warfarin dose by 33%–50%.
            (C) Simvastatin: Increased simvastatin exposure. Do not exceed dose of 20 mg/day.
            (D) Lovastatin: Increased lovastatin exposure. Do not exceed dose of 40 mg/day.
            (E) β-Blockers, non-DHP CCBs, clonidine, ivabradine: Additive bradycardia
         (9) Extensive monitoring for noncardiac adverse effects
            (A) Liver function tests (LFTs): Baseline and every 6 months
            (B) Thyroid function tests: Baseline and every 6 months
            (C) Chest radiography: Baseline and annually
            (D) ECG: Periodically
            (E) Pulmonary function tests (including Dl,CO [carbon dioxide diffusion in the lungs]): Baseline and for unexplained cough/dyspnea, chest radiographic abnormalities or clinical suspicion. Discontinue if pulmonary fibrosis occurs.
            (F) Ophthalmologic examination: Baseline (if visual impairment) and if patient has symptoms of visual impairment. Discontinue if optic neuritis occurs.
            (G) Skin toxicities: “Blue skin” syndrome and sunburn
            (H) Neurologic toxicity: Tremor, neuropathy
            (I) Nausea, vomiting
            (J) Adverse effects may require increased monitoring, dose reduction, or drug discontinuation
      (b) Sotalol: 50%–60% efficacy
         (1) Renal excretion. Dose adjustment and vigilat corrected QT (QTe) interval monitoring necessary in renal impairment. Recommended starting dose is 80 mg twice daily (unless creatinine clearance [CrCl] less than 60 mL/minute, then once daily).
         (2) Should be initiated in the hospital (minimum of 3-day stay), where QTc interval, serum electrolytes (e.g., K and magnesium), and renal function can be monitored
(3) Contraindicated in patients with HF (stable or unstable); CrCl less than 40 mL/minute; QTc interval greater than 450 milliseconds; and second- or third-degree AV block or sick sinus syndrome (in absence of pacemaker)

(4) Possesses nonselective β-blocking properties; may result in additive bradycardia with β-blockers, non-DHP CCBs, clonidine, ivabradine, and digoxin

(c) Dofetilide: 50%–60% efficacy

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

(2) Starting dose is selected based on renal function

(A) CrCl greater than 60 mL/minute: 500 mcg twice daily
(B) CrCl 40–60 mL/minute: 250 mcg twice daily
(C) CrCl 20–39 mL/minute: 125 mcg twice daily
(D) CrCl less than 20 mL/minute: Contraindicated

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

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

(5) Hepatically metabolized by CYP3A4

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

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

(8) May use in patients with HF

(9) Drug interactions

(A) Avoid concomitant use of the following drugs: cimetidine, verapamil, itraconazole, ketoconazole, hydrochlorothiazide, prochlorperazine, megestrol, dolugegravir, and trimethoprim alone or in combination with sulfamethoxazole

(B) Use CYP3A4 inhibitors, triamterene, metformin, and amiloride with caution: increased dofetilide exposure

(d) Dronedarone: 21%–25% efficacy

(1) Amiodarone analog lacking the iodine moiety that contributes to the thyroid toxicity of amiodarone

(2) Has electrophysiologic properties of classes I–IV

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

(4) Hepatically metabolized; CYP3A4 substrate; CYP3A4, CYP2D6, and P-gp inhibitor

(5) Half-life is 13–19 hours.

(6) Small increase in SCr by 0.1 mg/dL probably a result of inhibition of creatinine’s tubular secretion; rapid onset, will plateau after 7 days, and is reversible. Monitor SCr periodically.

(7) Acute kidney injury has also been reported, and it is usually reversible with drug discontinuation.

(8) Contraindicated in permanent AF; NYHA class II or III HF with recent decompensation necessitating hospitalization; NYHA class IV HF; second- or third-degree AV block or sick sinus syndrome (in absence of pacemaker); severe liver impairment, HR less than 50 beats/minute; concurrent use of strong CYP3A4 inhibitors or QTc interval–prolonging agents; history of amiodarone-induced hepatotoxicity or pulmonary toxicity; pregnancy; or QTc interval 500 milliseconds or greater
One trial found dronedarone less effective than amiodarone for the maintenance of SR, but with fewer adverse effects.

Drug interactions

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

Other safety issues

- **Liver injury**: According to postmarketing surveillance, dronedarone has been associated with rare but severe hepatic liver injury.
- **Pulmonary toxicity**: In postmarketing surveillance, cases of interstitial lung disease, including pneumonitis and pulmonary fibrosis, have been reported. Patients should report any new signs of dyspnea or nonproductive cough (Figure 4).

---

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

- **Dofetilide**
- **Flecainide**
- **Propafenone**
- **Sotalol**
- **Catheter ablation**
- **Amiodarone**

- **CHD** = coronary heart disease; **HF** = heart failure.

3. Antithrombotic therapy
   a. The average annual stroke rate is 5% per year without anticoagulation.
      i. A patient’s individual risk can vary from about 1% to 20% per year depending on risk factors.
      ii. This risk is independent of current cardiac status (i.e., SR or AF).
   b. Risk stratification and treatment determination is based on the CHA₂DS₂-VASc score (Tables 10–11). Of note, the 2018 CHEST guidelines for anticoagulation in atrial fibrillation no longer recommend antiplatelet therapy alone for prevention of stroke or systemic embolism.”

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

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

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

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

Table 11. Recommendations for Antithrombotic Therapy Based on CHA₂DS₂-VASc Score

<table>
<thead>
<tr>
<th>CHA₂DS₂-VASc Score = 0 (men) or 1 (women)</th>
<th>CHA₂DS₂-VASc Score = 1 (men) or 2 (women)</th>
<th>CHA₂DS₂-VASc Score ≥ 2 (men) or ≥3 (women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasonable to omit antithrombotic therapy</td>
<td>Antithrombotic therapy may be considered with a DOAC (preferred) or warfarin</td>
<td>Antithrombotic therapy with DOAC (preferred) or warfarin</td>
</tr>
</tbody>
</table>

OAC = oral anticoagulant.

c. Dabigatran (Tables 12 and 13)

Table 12. Comparison of the Direct Oral Anticoagulants

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

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

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

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

ii. Dose:
(a) CrCl greater than 30 mL/minute: 150 mg twice daily
(b) CrCl 15–30 mL/minute: 75 mg twice daily
(c) CrCl less than 15 mL/minute: No dosing recommendations available
(d) Swallow capsules whole (do not break, crush, or chew).

iii. Antidote: Idarucizumab
(a) Indicated for emergency surgery or urgent procedures or in life-threatening or uncontrolled bleeding.
(b) Dosing: Administer 5 g (as 2 separate 2.5-g doses no more than 15 minutes apart) intravenously. May consider a second dose if coagulation parameters re-elevate, clinically relevant bleeding occurs, or a second emergency surgery/urgent procedure is indicated

iv. Stability: Once a bottle is opened, the medication should be used within 4 months to maintain appropriate potency.
v. Converting from or to warfarin or parenteral anticoagulants (Box 1)

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

<table>
<thead>
<tr>
<th>Converting from dabigatran to warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt; 50 mL/min</td>
</tr>
<tr>
<td>CrCl 31–50 mL/min</td>
</tr>
<tr>
<td>CrCl 15–30 mL/min</td>
</tr>
<tr>
<td>CrCl &lt; 15 mL/min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Converting from dabigatran to parenteral anticoagulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients currently taking dabigatran, wait 12 hr (CrCl &gt; 30 mL/min) or 24 hr (CrCl &lt; 30 mL/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Converting from parenteral anticoagulants to dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start dabigatran 0–2 hr before the next dose of the parenteral drug was to have been administered (e.g., LMWH) or when a continuously administered parenteral drug is discontinued (e.g., intravenous UFH)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Converting from warfarin to dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue warfarin and start dabigatran when the INR &lt; 2.0</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 ≥2 days.

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

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

d. Rivaroxaban (Tables 12 and 13)

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

ii. Dose
   (a) CrCl greater than 50 mL/minute: 20 mg/day with evening meal
   (b) CrCl 15–50 mL/minute: 15 mg/day with evening meal
   (c) CrCl less than 15 mL/minute: Avoid use
   (d) Can be administered by nasogastric tube or gastric feeding tube (crush tablets and suspend in 50 mL of water). Tablets can also be crushed and mixed in applesauce.

iii. Antidote: Andexanet alfa
   (a) Indicated for drug action reversal due to life-threatening or uncontrolled bleeding related to rivaroxaban or apixaban
   (b) Dosing:
      (1) For patients receiving rivaroxaban 10 mg or less within less than 8 hours or unknown period of time: Initial, 400 mg IV bolus at target rate of 30 mg/min; follow with 4 mg/min continuous infusion for up to 120 mins.
      (2) For patients receiving rivaroxaban greater than 10 mg (or unknown dose) within less than 8 hours or unknown period of time: Initial, 800 mg IV bolus at target rate of 30 mg/min; follow with 8 mg/min continuous IV infusion for up to 120 minutes.
iv. Converting from or to warfarin or other anticoagulants (Box 2)

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

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

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

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

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

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

v. Drug interactions. Rivaroxaban is a substrate of CYP3A4/5 and P-gp.
(a) Combined strong dual inhibitors of CYP3A4 and P-gp (ketoconazole, ritonavir): Avoid administration of rivaroxaban.
(b) Combined strong dual inducers of CYP3A4 and P-gp (carbamazepine, phenytoin, rifampin, St. John’s wort): Avoid administration of rivaroxaban.
(c) Combined P-gp inhibitors and moderate CYP3A4 inhibitors (erythromycin) in the setting of renal impairment (CrCl 15 to <80 mL/minute): Avoid administration of rivaroxaban.

e. Apixaban (Tables 12 and 13)
(i) Factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF; demonstrated superiority over warfarin for efficacy
(ii) Dose
(a) 5 mg twice daily unless:
   (1) In patients with at least two of the following characteristics (age 80 years or older, body weight of 60 kg or less, or SCr of 1.5 mg/dL or greater) the recommended dose is 2.5 mg twice daily.
   (2) CrCl less than 15 mL/minute, no specific recommendations
   (3) End-stage renal disease maintained on hemodialysis, 5 mg twice daily. In patients with end-stage renal disease maintained with hemodialysis who are 80 years and older and/or weigh 60 kg or less, 2.5 mg twice daily
(b) Can be crushed and suspended in water, dextrose 5% in water, apple juice, or apple sauce and administered orally
(c) Can be administered by nasogastric tube (crush tablets and suspend in 60 mL water or dextrose 5% in water and administer immediately)
(iii) Antidote: Andexanet alfa
(a) Indicated for drug action reversal due to life-threatening or uncontrolled bleeding related to rivaroxaban or apixaban
Cardiology II

ACCP Updates in Therapeutics® 2019: Pharmacotherapy Preparatory Review and Recertification Course

(b) Dosing:
   (1) For patients receiving apixaban 5 mg or less within less than 8 hours or unknown period of time: Initial, 400 mg IV bolus at target rate of 30 mg/min; follow with 4 mg/min continuous infusion for up to 120 minutes.
   (2) For patients receiving apixaban greater than 5 mg (or unknown dose) within less than 8 hours or unknown period of time: Initial, 800 mg IV bolus at target rate of 30 mg/min; follow with 8 mg/min continuous IV infusion for up to 120 minutes.

iv. Converting from or to warfarin or other anticoagulants (Box 3)

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

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

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

<table>
<thead>
<tr>
<th>Converting from warfarin to apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin should be discontinued and apixaban initiated when INR &lt; 2.0</td>
</tr>
</tbody>
</table>

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

INR = international normalized ratio

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

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

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

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

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

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

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

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

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

**Warfarin**

i. Inhibits vitamin K–dependent clotting factors II, VII, IX, X. Also inhibits anticoagulant proteins C and S. Racemic mixture of R- and S-isomers:
   (a) S-isomer more potent vitamin K antagonist
   (b) S-isomer metabolized primarily by CYP2C9
   (c) R-isomer metabolized primarily by CYP3A4

ii. Dosing is based on what is needed to achieve an INR goal of 2–3 for patients with nonvalvular AF. For patients with mitral stenosis, prosthetic heart valves, prior thromboembolism, or persistent atrial thrombus on TEE, an INR goal of 2.5–3.5 or even higher may be indicated.

iii. Initial starting dose is usually 5 mg/day. Lower starting dose (2–3 mg/day) should be considered in patients with the following: advanced age, low body weight, drug interactions, malnutrition, HF, hyperthyroid state, low albumin, or liver disease.
   (a) Half-lives of vitamin K–dependent clotting factor VII, 6 hours; factor IX, 24 hours; factor X, 36 hours; factor II, 72 hours
   (b) Adjusting dose: Watch for trends; remember that the INR seen today is the result of the doses given in the past 4–5 days. It takes 5–7 days to reach full effect, given the half-life of factor II.
   (c) If INR is out of therapeutic range, increase or decrease cumulative weekly warfarin dose by 5%–20% depending on INR; if INR is high, hold one or two doses and resume at a lower dose.
(d) If INR was previously stable or therapeutic and single out-of-range INR is 0.5 or less above or below therapeutic range, the current dose can be continued; recheck INR within 1–2 weeks.

(e) In general, no need to adjust if INR is within 0.1 of goal (but monitor more closely)

iv. Place in therapy: Consider individual clinical features. May be optimal for patients with severe renal impairment, mechanical heart valves, and valvular AF or for those who are stable on warfarin or are not otherwise candidates for direct oral anticoagulant therapy

v. Antidote: Vitamin K. Four-factor prothrombin complex may also be used to reverse bleeding

vi. Drug interactions

(a) Reduced warfarin absorption (e.g., cholestyramine, sucralfate)

(b) Enzyme induction (decreases INR and warfarin effects): CYP3A4 inducers (e.g., rifampin, carbamazepine, phenobarbital, St. John's wort)

(c) Enzyme inhibition (increases INR and warfarin effects)

1) S-warfarin (CYP2C9 inhibitors) (e.g., metronidazole, trimethoprim/sulfamethoxazole, fluconazole, isoniazid, fluoxetine, sertraline, amiodarone, clopidogrel)

2) R-warfarin (CYP3A4/5 inhibitors) (e.g., clarithromycin, erythromycin, “azole” antifungals, nefazodone, fluoxetine, amiodarone, cyclosporine, sertraline, grapefruit juice, ciprofloxacin, protease inhibitors, diltiazem, verapamil, isoniazid, metronidazole)

(d) Drugs with antiplatelet effects (e.g., gingko, garlic, aspirin, NSAIDs, clopidogrel, ticagrelor, prasugrel, selective serotonin reuptake inhibitors); NSAIDs and aspirin also increase the risk of ulcers, providing a site from which to bleed.

(e) Drugs that reduce warfarin clearance (e.g., propafenone)

(f) Drugs that increase the degradation of clotting factors (e.g., levothyroxine)

(g) Drugs that reduce vitamin K synthesis in the intestinal flora (e.g., antibiotics)

vii. Bleeding: incidence 2.4%–29%, life threatening 2%–8% (epistaxis, hematuria, GI hemorrhage, bleeding gums). Easy bruising often occurs with therapeutic INR.

(a) Minor hemorrhage increased with therapeutic warfarin therapy

(b) Major hemorrhage not increased with warfarin therapy at INR 2–3

(c) Risk of intracranial hemorrhage increased with INR greater than 4

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**Patient Case**

5. H.D. is a 67-year-old man with a history of HTN, moderate mitral valve insufficiency, and AF for 4 years. His medications include ramipril 5 mg twice daily, sotalol 120 mg twice daily, digoxin 0.125 mg/day, and warfarin 5 mg/day. He visits his primary care physician today after being discharged from the emergency department with increased fatigue on exertion, palpitations, and lower extremity edema. His vital signs today include BP 115/70 mm Hg and HR 88 beats/minute, and all laboratory results are within normal limits; however, his lower extremity edema has worsened. His INR is 2.8. His ECG shows AF. An echocardiogram reveals an LVEF of 35%–40%. H.D.’s physician would like to continue a rhythm control approach. What is the best treatment option for managing his AF?

A. Discontinue sotalol and begin metoprolol succinate 12.5 mg/day.

B. Discontinue sotalol and begin dronedarone 400 mg twice daily.

C. Discontinue sotalol and begin amiodarone 400 mg twice daily, tapering to goal dose of 200 mg/day for the next 6 weeks.

D. Continue sotalol and add metoprolol tartrate 25 mg twice daily.
D. Nonpharmacologic therapies (procedures)
   1. Electrical cardioversion (low-energy cardioversion; sedation highly desirable)
   2. AV nodal ablation: Ablate AV node and chronically pace the ventricles.
   3. Pulmonary vein ablation: Ablates the origin of the abnormal atrial foci, which is often near the pulmonary vein–atrial tissue intersection.

III. HYPERTENSION

Definition: HTN is a persistent, nonphysiologic elevation of BP; it is defined as (1) having an SBP of 140 mm Hg or greater; (2) having a DBP of 90 mm Hg or greater; (3) taking antihypertensive medication; or (4) having been told at least twice by a physician or other health professional that one has HTN.

A. Background
   1. Prevalence
      a. Most common chronic disease in the United States
      b. Affects 46% of the population
      c. Prevalence increases with age
      d. Major modifiable risk factor for CV disease and stroke
   2. Etiology
      a. Essential HTN: 90% (no identifiable cause)
         i. Obesity is a contributor
         ii. Evaluate Na intake
      b. Secondary HTN
         i. Primary aldosteronism
         ii. Renal parenchymal disease
         iii. Renal artery stenosis
         iv. Obstructive sleep apnea
         v. Cushing syndrome
         vi. Thyroid or parathyroid disease
         vii. Medications (e.g., cyclosporine, NSAIDs, sympathomimetics)
         viii. Pheochromocytoma
   3. Diagnosis
      a. Periodic screening for all people older than 21 years
      b. Patient should be seated quietly in chair for at least 5 minutes.
      c. Use appropriate cuff size (bladder length at least 80% the circumference of the arm).
      d. Take BP at least twice, separated by at least 2 minutes.
      e. The average BP on two separate visits is required to diagnose HTN accurately.
      f. Home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) are recommended to confirm diagnosis, screen for white-coat HTN, and screen for masked HTN
         i. White-coat HTN: Office blood pressure is 130/80-160/100 mm Hg after a 3-month trial of lifestyle modification but with daytime ABPM or HBPM blood pressure less than 130/80 mm Hg
         ii. Masked HTN: Office blood pressure is 120-129/less than 80 mm Hg after a 3-month trial of lifestyle modification; daytime ABPM or HBPM blood pressure of 130/80 or greater
4. Benefits of treating elevated BP
   a. Decreased risk of stroke (by 35-40%)
   b. Decreased risk of MI (by 20-25%)
   c. Decreased risk of HF (by 50%)
5. Effects of lifestyle modifications on BP (Table 14)

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

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

B. Therapeutic management
   1. Patient classification and management in adults: (Table 15)

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>and&lt; 80</td>
</tr>
<tr>
<td>Elevated</td>
<td>120-129</td>
<td>and&lt; 80</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>139-139</td>
<td>or 80-89</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥140</td>
<td>or ≥ 90</td>
</tr>
<tr>
<td>Hypertensive urgency/ emergency</td>
<td>&gt;180</td>
<td>or &gt;120</td>
</tr>
</tbody>
</table>

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure
Patient Cases

6. W.D. is a 55-year-old white female who was recently admitted to the hospital with acute myocardial infarction which was treated with a stent. She has a past medical history of HTN and GERD. She is visiting your clinic today for management of her cardiovascular medications. Her vitals today include BP 152/86 mm Hg and HR 82 beats/minute. Her labs are all WNL, including Na 140 mEq/L, K 4.3 mEq/L, and SCr 1.0 mg/dL. Her current medication regimen includes clopidogrel 75 mg daily, aspirin 81 mg daily, and atorvastatin 40 mg daily. What is the most appropriate approach to manage her HTN?
   A. Add carvedilol monotherapy
   B. Add lisinopril and metoprolol
   C. Add amlodipine and metoprolol
   D. Add lisinopril monotherapy

7. T.J. is a 45-year-old African American woman presenting for routine follow-up of her DM2. She has no other medical history. Her blood pressure today (average of 2 readings) is 138/88 mm Hg. Her HR is 77 beats/minute. Her BP at her last visit was 136/85 mm Hg. Her current medications include glyburide 5 mg daily. Her labs include Na 140 mEq/L, K 4.0 mEq/L, Cl 102 mEq/L, bicarbonate 28 mEq/L, blood urea nitrogen 14 mg/dL, SCr 0.8 mg/dL, and 24-hour urine albumin 16 mg/24 hours. What is the best approach for managing her HTN?
   A. Begin diet and lifestyle modifications only
   B. Begin lifestyle modifications and add amlodipine 5 mg daily
   C. Begin lifestyle modifications and add lisinopril 2.5 mg daily
   D. Begin lifestyle modifications and add lisinopril 2.5 mg daily plus hydrochlorothiazide 12.5 mg daily

2. The 2017 11/AHA HTN guideline blood pressure thresholds and goals are listed in Table 16.

Table 16. BP Thresholds for Goals of Pharmacologic Therapy in Patients with HTN According to Clinical Condition

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>BP Threshold, mm Hg</th>
<th>BP Goal, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical CVD or 10-year ASCVD risk ≥10%</td>
<td>≥130/80</td>
<td>&lt;130/80 for all</td>
</tr>
<tr>
<td>No clinical CVD and 10-year ASCVD risk &lt;10%</td>
<td>≥140/90</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥130/80</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>≥130/80</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease after renal transplantation</td>
<td>≥130/80</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>≥130/80</td>
<td></td>
</tr>
<tr>
<td>Stable ischemic heart disease</td>
<td>≥130/80</td>
<td></td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>≥140/90</td>
<td></td>
</tr>
<tr>
<td>Secondary stroke prevention (lacunar)</td>
<td>≥130/80</td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>≥130/80</td>
<td></td>
</tr>
<tr>
<td>Older persons (≥65 years; noninstitutionalized,</td>
<td>≥130 (SBP)</td>
<td>&lt;130 (SBP)</td>
</tr>
<tr>
<td>ambulatory, community-living)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*According to the 2017 ACC/AHA HTN guideline; 2018 ADA guideline does not agree.
ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CVD = cardiovascular disease; SBP = systolic blood pressure.
3. Blood pressure treatment strategies according to BP and ASCVD risk are located in Figure 5.

![Figure 5. BP treatment strategies according to BP level and ASCVD risk.](image)

*Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 HTN and an average blood pressure of greater than 20/10 mm Hg above their blood pressure target. ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure.


4. Select an appropriate drug therapy regimen
   a. Initiating therapy with a single antihypertensive drug is reasonable in adults with stage 1 HTN and a BP goal of less than 130/80 mm Hg
   b. Initiating antihypertensive drug therapy with two first-line agents of different classes is recommended in adults with stage 2 HTN and an average BP greater than 20/10 mm Hg above their BP target
   c. First-line agents include thiazide diuretics, CCBs, and ACEIs or ARBs.
d. First-line agents for patients with comorbidities is described in Figure 6.

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

Initial medication choice based on disease state

- **Diabetes**
  - ACEI, ARB, CCB, or thiazide; ACEI/ARB preferred in albuminuria

- **CKD**
  - ACEI or ARB in patients with albuminuria

- **Stroke or TIA**
  - Thiazide, ACEI, or ARB

- **Coronary disease**
  - BB + ACEI or ARB

- **HFrEF**
  - ACEI, ARB, or ARNI; BB; AA; as needed diuretic

- **HFpEF**
  - Diuretic

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

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

5. Considerations with specific antihypertensive agents

a. **β-Blockers**
   i. Caution with asthma or severe chronic obstructive pulmonary disease (especially higher doses) because of pulmonary β-receptor blockade, especially with nonselective β-blockers or high-dose selective β-blockers.
   ii. Greater risk of developing DM than with an ACE inhibitor, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity)
   iii. Can mask some signs of hypoglycemia in patients with DM
   iv. Can cause depression

b. **Thiazides**
   i. Can worsen gout by increasing serum uric acid
   ii. Not recommended for patients with a CrCl less than 30 mL/minute because of reduced efficacy
   iii. Greater risk of developing DM than with ACE inhibitor, ARB, and CCB; use caution in patients at high risk of DM (e.g., family history, obesity)
   iv. Can assist in the management of osteoporosis by preventing urine calcium loss

c. **ACE inhibitors and ARBs**
   i. Contraindicated in pregnancy
   ii. Contraindicated with bilateral renal artery stenosis
   iii. Monitor K closely, especially if renal impairment exists or another K-sparing drug or K supplement is used.

d. **Direct renin antagonist (aliskiren)**
   i. Contraindicated in pregnancy
   ii. Contraindicated in patients with DM when used in combination with ACE inhibitors or ARBs because of increased risk of renal impairment, hyperkalemia, and hypotension
iii. Avoid use in combination with cyclosporine or itraconazole.
iv. Avoid concurrent use with ACE inhibitors or ARBs in patients with renal impairment (CrCl less than 60 mL/minute).
e. Calcium channel blockers
i. Dihydropyridine CCBs
   (a) Amlodipine, felodipine, nifedipine
   (b) Monitor for peripheral edema, reflex tachycardia, and orthostatic hypotension
   (c) Useful for isolated systolic hypertension or use in African American patients
ii. Nondihydropyridine CCBs
   (a) Diltiazem, verapamil
   (b) Indicated in hypertensive patients with comorbid conditions which would benefit from HR reduction (e.g., atrial fibrillation, stable angina)
   (c) Contraindicated in heart block and sick sinus syndrome
   (d) Potential drug interactions due to CYP450 inhibition

6. Considerations within specific patient populations
a. Patients with CHD: Potent vasodilators (hydralazine, minoxidil, and DHP CCBs) may cause reflex tachycardia, thereby increasing myocardial oxygen demand; can attenuate this by also using an AV nodal blocker (β-blocker or non-DHP CCB)
b. Older adult patients:
   i. Treatment of HTN with an SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community-dwelling adults (65 and older) with an average SBP of 130 mm Hg or greater
   ii. For older adults (65 and older) with HTN and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk-benefit is reasonable for decisions regarding intensity of blood pressure lowering and choice of antihypertensives
   iii. The SPRINT trial published in late 2015 showed that targeting an SBP of less than 120 mm Hg, compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major CV events and death from any cause among patients at high risk of CV events but without DM. Twenty-five percent of the study population was older than 75 years.
   iv. Caution with antihypertensive agents and orthostatic hypotension
c. Black patients: β-Blockers and ACE inhibitors are generally less effective as monotherapy than in non–black patients. In black adults with HTN but without HF or CKD, including those with diabetes mellitus, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. β-blockers and ACE inhibitors should still be used if comorbid conditions dictate.
d. Women
   i. Oral estrogen-containing contraceptives can increase BP, and the risk can increase with the duration of use.
   ii. HTN increases the risk to mother and fetus in women who are pregnant. Preferred medications include methyldopa, nifedipine and labetalol. ACE inhibitors, ARBs, and aliskiren should not be used because of the potential for fetal defects.

7. Monitoring
a. Have the patient return in 4 weeks to assess efficacy (sooner if clinically indicated).
b. If there is an inadequate response with the first agent with optimal dosing (and adherence is verified) and no compelling indication exists, initiate therapy with a drug from a different class while continuing initial therapy.
8. Resistant HTN
   a. Confirm diagnosis
      i. Office BP of 130/80 mm Hg or greater and patient taking at least three antihypertensive medications at optimal doses, including a diuretic (confirmed adherence) OR
      ii. Office BP of <130/80 mm Hg but patient requires at least four antihypertensive medications
   b. Exclude pseudoresistance
      i. Ensure accurate office BP readings
      ii. Exclude white-coat HTN
      iii. Ensure adherence
   c. Identify and reverse contributing factors
      i. Lifestyle factors
         (a) Obesity
         (b) High-salt, low-fiber diet
         (c) Physical inactivity
         (d) Excessive alcohol use
      ii. Interfering medications
         (a) NSAIDs
         (b) Sympathomimetics
         (c) Stimulants
         (d) Oral contraceptives
   d. Screen and treat for secondary causes of HTN (described earlier)
   e. Assess for target organ damage
   f. Pharmacological treatment
      i. Maximize diuretic therapy
         (a) Use thiazide or thiazide-like diuretics if eGFR > 25-30 mL/min/m²
            (1) Chlorthalidone and indapamide have the most evidence for reducing cardiovascular outcomes
            (2) Chlorthalidone is more effective at inducing predictable natriuresis in patients with an eGFR 30-45 mL/min/m²
         (b) Use loop diuretics if eGFR < 30 mL/min/m²
      ii. Add MRA (spironolactone or eplerenone)
      iii. Alter dosing times to include a nocturnal dose or divide doses of drugs with half-lives <12-15 hours
      iv. Add other agents from different drug classes
      v. Addition of hydralazine or minoxidil requires concomitant use of a β-blocker and diuretic
   g. Follow-up
      i. Ensure attainment of target BP after six months of therapy
      ii. If patient not at goal, refer to appropriate specialists

IV. DYSLIPIDEMIA

A. The AHA/ACC released updated Cholesterol Guidelines in 2018 in conjunction with 10 other organizations. Major changes in new guidelines:
   1. Emphasis on personalized risk assessment and shared decision making using tools listed in (D) below
   2. Re-introduction of LDL-C and non-HDL-C goals
   3. Recommendations for statin and nonstatin therapies
B. Nonpharmacological recommendations
1. Lifestyle modification is cornerstone of initial intervention
   a. Recommend healthy diets such as the Dietary Approaches to Stop Hypertension (DASH) diet or the Mediterranean Diet
   b. Emphasize consumption of fruits, vegetables, whole grains, low-fat dairy products, skinless poultry and fish, nuts and legumes, and non-tropical vegetable oils
   c. Limit sweets, sugar-sweetened beverages, and red meats
   d. Lower intake of saturated fats and replace with unsaturated fats (especially polyunsaturated fats)

2. Regular exercise
   3. Smoking cessation

C. Pharmacologic recommendations
1. Therapy recommendations are divided into patient management groups:
   a. Secondary ASCVD prevention
   b. Severe hypercholesterolemia (LDL-C ≥190 mg/dL)
   c. Diabetes mellitus (DM)
   d. Primary prevention

2. Pharmacologic management of dyslipidemia is detailed in Figure 7, and general principles are described below:
   a. First, initiate statin therapy if indicated. Optimize statin therapy (high intensity or maximally tolerated dose) before adding nonstatin therapy
   b. Second, add ezetimibe if indicated
   c. Third, consider PCSK9-inhibitors (PCSK9-I)

3. Special populations
   a. Patients age >75 years
      i. Reasonable to initiate a moderate-intensity statin or continue a moderate- or high-intensity statin if benefits outweigh risks
      ii. Reasonable to discontinue statin therapy if patients have functional decline, multimorbidity, frailty, or reduced life expectancy limits potential benefits
   b. Hypertriglyceridemia
      i. Primary goal is to prevent pancreatitis
      ii. Evaluate for secondary causes (Table 17)

<table>
<thead>
<tr>
<th>Table 17. Common Secondary Causes of Elevated LDL-C and TG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Dietary influences</td>
</tr>
<tr>
<td>Disease states and medical conditions</td>
</tr>
</tbody>
</table>

LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.
Figure 7: Algorithm for statin and non-statin therapy recommendations based on patient management group

1. Statin therapy

   - High-intensity statin
   - Moderate or high-intensity statin
   - Maximal tolerated statin therapy

2. Consider ezetimibe after statin therapy if:

   - LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
   - Age >75 years

3. Consider PCSK9 inhibitor after statin and ezetimibe if:

   - Very high risk (history of multiple major ASCVD events or one major event plus multiple high-risk conditions)
     - LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
     - Age 57 years
   - High-intensity statin
     - LDL-C ≥70 mg/dL
     - Age >75 years
   - Moderate or high-intensity statin
     - LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
     - Age 20-39 years
   - Severe hypercholesterolemia (LDL-C ≥190 mg/dL and age 20-75 years)

4. Consider additional therapies in ASCVD or DM if:

   - Age 40-75 years
   - 10-year ASCVD risk ≥20%
   - DM

5. Continue previously initiated statin therapy if benefits outweigh risks.
### Figure 7. Algorithm for statin and non-statin therapy recommendations based on patient management group

<table>
<thead>
<tr>
<th>Patient Management Group</th>
<th>1. Statin therapy</th>
<th>2. Consider ezetimibe after statin therapy if:</th>
<th>3. Consider PCSK9-I after statin and ezetimibe if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (&lt;5%)</td>
<td>Lifestyle modifications only; reassess every 4-6 years</td>
<td>If risk enhancers present, consider moderate-intensity statin</td>
<td></td>
</tr>
<tr>
<td>Borderline risk (5.7-6.4%)</td>
<td></td>
<td>If additional LDL-C lowering warranted but high-intensity statin therapy not advisable or tolerated, consider ezetimibe or BAS</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk (7.5-19.9%)</td>
<td>Moderate intensity statin if benefits &gt; risks (goal LDL-C ↓ 30-49%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk (≥20%)</td>
<td>High intensity statin (goal LDL-C ↓ ≥50%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key:  
- **Class I (strong) recommendation**  
- **Class IIa (moderate) recommendation; therapy is reasonable**  
- **Class IIb (weak) recommendation; therapy may be considered**  

ABI = ankle-brachial index; ASCVD = atherosclerotic cardiovascular disease; BAS = bile acid sequestrant; DM = diabetes mellitus; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCE = Pooled Cohort Equation; PCSK9-I = PCSK9 inhibitor

- **Major ASCVD events are acute coronary syndrome (ACS) within the past 12 months, other history of myocardial infarction (MI), history of ischemic stroke, and symptomatic peripheral arterial disease**
- **High risk conditions are age ≥65 years, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), diabetes mellitus (DM), hypertension, chronic kidney disease (eGFR 15-59 mL/min/1.73m²), current smoking, history of congestive heart failure, and persistently elevated LDL-C ≥ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe**
- **Clinical evidence supports addition of PCSK9-I after maximally tolerated statin therapy, but adding ezetimibe first is more cost effective**
- **If risk decision is uncertain (especially borderline and intermediate risk patients), consider measuring coronary artery calcium**

iii. Moderate hypertriglyceridemia (triglycerides [TG] 175-499 mg/dL)
   (a) Address and treat lifestyle factors, comorbidities, and medications which increase TGs
   (b) If persistently elevated and ASCVD risk ≥7.5%, consider initiation or intensification of statin therapy

iv. Severe hypertriglyceridemia (TG ≥ 500 mg/dL)
   (a) If persistently elevated and ASCVD risk ≥7.5%, consider initiation or intensification of statin therapy
   (b) Reasonable to initiate fibrate therapy to prevent acute pancreatitis, especially if fasting TG ≥ 1000 mg/dL

v. Expected changes in TG concentrations with drug therapy (Table 18)

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

TG = triglycerides

Table 18. Effect of Lipid-Lowering Medications on TG

D. Risk assessment tools for primary prevention

1. Risk discussions and shared decision making with patients should consider whether lifestyle and ASCVD risk factors have been addressed, cost considerations, and a discussion of the potential benefits and adverse events of drug therapy. Patients and health care professionals should work together to establish a customized cholesterol management plan.

2. Pooled Cohort Equation (PCE) to estimate 10-year ASCVD risk
   a. Measures hard ASCVD events: fatal and nonfatal MI and stroke
   b. Assists with identifying higher-risk patients for statin therapy
   c. Should not be used for patients with clinical ASCVD
   d. Available at http://tools.acc.org/ASCVD-Risk-Estimator/
   e. Components of PCE:
      i. Sex
      ii. Age
      iii. Race
      iv. TC
      v. HDL-C
      vi. SBP
      vii. Receiving treatment for high BP
      viii. DM
      ix. Smoker

3. Risk-enhancing factors
   a. Family history of premature ASCVD (males <55 years, females <65 years)
   b. Primary hypercholesterolemia (LDL-C 160-189 mg/dL or non-HDL-C 190-219 mg/dL)
   c. Metabolic syndrome
   d. Chronic kidney disease
e. Chronic inflammatory conditions such as psoriasis, rheumatoid arthritis, HIV/AIDS
f. History of premature menopause (age <40 years)
g. History of preeclampsia
h. High-risk race/ethnicity (e.g., South Asian ancestry)
i. Elevated TG ≥175 mg/dL
j. Elevated biomarkers such as high-sensitivity C-reactive protein, lipoprotein (a), apolipoprotein B
k. Ankle-brachial index <0.9

4. Coronary artery calcium (CAC) score for additional risk-stratification
   a. If risk decision is uncertain (especially borderline and intermediate risk patients), consider measuring coronary artery calcium
   b. Score = 0: consider no statin (unless DM, family history of premature coronary heart disease, or cigarette smoking present)
   c. Score = 1-99: favors statin if age ≥55
   d. Score ≥100 or ≥75th percentile: favors statin

E. Monitoring
   1. Measure fasting lipids 4-12 weeks after therapy initiation
   2. Measure fasting lipids every 3-12 months thereafter
   3. Periodically re-assess risk factors for ASCVD

F. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)
   1. General approach to initiating statin therapy:
      a. Fasting lipid panel
         i. If LDL-C is higher than 190 mg/dL, evaluate for secondary causes. If primary, screen for familial hypercholesterolemia.
         ii. If TG 500 mg/dL or higher, treat hypertriglyceridemia
      b. Alanine aminotransferase (ALT)
         i. Evaluate patients with unexplained ALT more than 3x upper limit of normal
      c. Hemoglobin A1C
      d. Creatine kinase (if indicated)
      e. Evaluate for secondary causes or conditions that may affect statin safety
   2. Efficacy
      a. Role of nonstatin therapies for
      b. When selecting a statin, consider its intensity (Table 19).
      c. Reduce LDL-C by 24%–60%.
      d. Reduce TG by 7%–30%.
      e. Raise HDL-C by 5%–15%.
      f. Reduce major coronary events.
      g. Reduce CHD mortality.
      h. Reduce coronary procedures (percutaneous coronary intervention [PCI] or coronary artery bypass grafting).
      i. Reduce stroke.
      j. Reduce total mortality.
Table 19. Relative LDL-C-Lowering Efficacy of Statins

<table>
<thead>
<tr>
<th>Atorva (mg)</th>
<th>Fluva (mg)</th>
<th>Pitava (mg)</th>
<th>Lova (mg)</th>
<th>Prava (mg)</th>
<th>Rosuva (mg)</th>
<th>Simva (mg)</th>
<th>%↓ LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>20–40</td>
<td>1</td>
<td>20</td>
<td>10–20</td>
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<td>10</td>
<td>30</td>
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<tr>
<td>10</td>
<td>80</td>
<td>2</td>
<td>40</td>
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<td>20</td>
<td>38</td>
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<td>4</td>
<td>80</td>
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<td>5</td>
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<td>80</td>
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<td>---</td>
<td>---</td>
<td>20</td>
<td>---</td>
<td>55</td>
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<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>40</td>
<td>---</td>
<td>63</td>
</tr>
</tbody>
</table>

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

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


3. Mechanism of action: Inhibits enzyme responsible for converting HMG-CoA to mevalonate (rate-limiting step in production of cholesterol)
4. Main adverse effects and monitoring
   a. Myopathy (can check creatine kinase [CK] at baseline and then only if muscle symptoms occur; no regular monitoring)
   b. Elevated liver enzymes
      i. Obtain LFTs at baseline in all patients
      ii. Perform repeated LFTs only when clinically indicated.
      iii. Monitor for symptoms of hepatic injury.
5. Absolute contraindications
   a. Active liver disease, unexplained persistent elevations in hepatic transaminases
   b. Pregnancy
   c. Nursing mothers
   d. Certain medications (agent-specific; see drug interactions below)
6. Select drug interactions (see Table 20)
   a. Fibrates: Increased risk of myopathy and rhabdomyolysis when coadministered with statins. Risk is greater with gemfibrozil than with fenofibrate.
   b. Niacin: Doses greater than 1 g/day increase the risk of myopathy and rhabdomyolysis when used concomitantly with statins; risk is lower than with fibrates; statins and niacin are commonly used together; monitor for muscle pain.
7. Differences exist between statins in regard to pharmacokinetics and renal dosing (Tables 21 and 22)
Table 20. Select Drug Interactions with Statins

<table>
<thead>
<tr>
<th>Drug</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>Daily dose NTE 40 mg</td>
<td>Daily dose NTE 20 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodipine</td>
<td></td>
<td>Daily dose NTE 20 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobicistat-containing products</td>
<td>CI</td>
<td>CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colchicine</td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Use with caution</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Avoid use</td>
<td>Daily dose NTE 20 mg</td>
<td>CI</td>
<td>Daily dose NTE 20 mg BID</td>
<td>CI</td>
<td>Avoid use</td>
<td>Daily dose NTE 5 mg</td>
</tr>
<tr>
<td>Danazol</td>
<td>Daily dose NTE 20 mg</td>
<td>CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Daily dose NTE 20 mg</td>
<td>Daily dose NTE 10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>CI</td>
<td>Daily dose NTE 40 mg (clarithromycin)</td>
<td>CI</td>
<td>Daily dose NTE 1 mg (erythromycin)</td>
<td>Daily dose NTE 20 mg (clarithromycin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>CI</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td>Daily dose NTE 10 mg</td>
</tr>
<tr>
<td>Grapefruit juice (&gt; 1 quart per day)</td>
<td>Avoid use</td>
<td>Avoid use</td>
<td></td>
<td></td>
<td>Avoid use quantities (&gt; 1.2 L/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole Itraconazole</td>
<td>CI (itraconazole, ketoconazole, posaconazole, and voriconazole)</td>
<td>CI (itraconazole, ketoconazole, posaconazole, and voriconazole)</td>
<td>Daily dose NTE 20 mg BID (fluconazole)</td>
<td>Daily dose NTE 20 mg (itraconazole)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lomitapide</td>
<td>Daily dose NTE 20 mg (or 40 mg if tolerated 80 mg for ≥1 yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td>CI</td>
<td>CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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>Use with caution</td>
<td></td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td>CI</td>
<td>CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Consider dose adjustment</td>
<td>Daily dose NTE 20 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily dose NTE 2 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

N/A = not applicable.

Table 22. Dosing of Statin Agents in CKD

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


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

CrCl = creatinine clearance; NTE = not to exceed

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

H. PCSK9 Inhibitors
1. Efficacy: Lower LDL-C by an additional 45%–68% when combined with statin therapy; reduce CV events when added to statin therapy FOURIER and ODYSSEY OUTCOMES trials
2. Mechanism of action: Monoclonal antibodies that inhibit a protein called PCSK9, increasing cholesterol clearance from the liver
3. Both indicated for heterozygous familial hypercholesterolemia or clinical ASCVD; evolocumab also indicated for homozygous familial hypercholesterolemia (HoFH)
4. PCSK9 Inhibitors are only indicated for select patients already receiving maximally tolerated statin therapy and ezetimibe with either clinical ASCVD at very high risk or severe hypercholesterolemia in the 2018 ACC/AHA cholesterol guidelines (Figure 7)

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

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

I. Bile acid sequestrants (cholestyramine, colestipol, colesevelam)

1. Efficacy
   a. Reduce LDL-C by 15%–27%.
   b. Raise HDL-C by 3%–5%.
   c. May increase TG concentrations.
   d. Reduce major coronary events.
   e. Reduce CHD mortality.

2. Mechanism of action: Bind to bile acids to disrupt 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 many drugs including: warfarin, amiodarone, levothyroxine, ezetimibe, digoxin, and thiazides; administer drugs 1–2 hours before or 4 hours after bile acid sequestrant

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

J. Niacin (Table 23)

1. Efficacy
   a. Lowers LDL-C by 5%–25%
   b. Lowers TG by 20%–50%
   c. Raises HDL-C by 15%–35%
   d. Reduces major coronary events
   e. Lowers lipoprotein (a)

2. Mechanism of action: Inhibits mobilization of free fatty acids from peripheral adipose tissue to the liver and reduces synthesis of TG, very-low-density lipoproteins, and LDL-C

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

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

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

6. Contraindications: liver disease and active peptic ulcer disease. Caution in patients predisposed to gout

7. Flushing can be minimized by taking aspirin or an NSAID 30–60 minutes before niacin, taking at bedtime with food, using slow titration, and avoiding hot beverages, spicy foods, and hot showers around the time of administration.

8. According to the 2018 AHA/ACC cholesterol guidelines, there are no clear indications for routine niacin use for reduction of LDL-C.
Table 23. Niacin Formulations

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

K. Fibrates
1. Efficacy
   a. Lower LDL-C by 5%–20% (with normal TG)
   b. May raise LDL-C with very high TG
   c. Lower TG by 20%–50%
   d. Raise HDL-C by 10%–20%
2. Mechanism of action: Reduces rate of lipogenesis in the liver
3. Adverse effects and monitoring: Dyspepsia, gallstones, myopathy, increased hepatic transaminases. Monitor LFTs every 3 months during first year and then periodically.
4. Contraindications: Severe renal or hepatic disease, pre-existing gallbladder disease
5. Indicated for treatment of severe hypertriglyceridemia, especially in patients with TG ≥ 1000 mg/dL

L. Omega-3 fatty acids
1. Contain varying ratios of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
   a. Omega-3 acid ethyl esters: DHA and EPA
   b. Icosapent ethyl: EPA only
   c. Omega-3 carboxylic acid: DHA and EPA
2. Efficacy
   a. Lowers TG by 26%–45%
   b. Can raise LDL-C when TG concentrations are high
   c. Raises HDL-C by 5%–14%
3. Mechanism of action: Reduction of hepatic production of very-low-density lipoproteins; possible reduction in hepatic synthesis of TG; increased hepatic β-oxidation
4. Adverse effects: Arthralgia, GI effects (e.g., burping, taste perversion, dyspepsia); at more than 3 g/day, bleeding (because of inhibition of platelet aggregation)
5. Dose: 2–4.8 g/day as a single dose or in two divided doses

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

8. Available only through the Risk Evaluation and Mitigation Strategy (REMS) program

9. Dose: 5 mg once daily, can be titrated to 60 mg/day

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 hypertension, DM, and asthma. She smokes one pack of cigarettes and drinks three beers per day. Her mother had HTN and suffered an MI at age 42 years. Her father had HTN and DM. Her medications are albuterol metered dose inhaler, lisinopril, metformin, linagliptin, and calcium carbonate antacids. Her vital signs include BP 134/84 mm Hg and HR 75 beats/minute. Her laboratory results are as follows: HDL-C 38 mg/dL, LDL-C 134 mg/dL, TG 186 mg/dL, TC 209 mg/dL, and hemoglobin A1C 8.6%. Her pooled cohort equation estimates a 10-year ASCVD risk of 27.8%. What is the most appropriate next step for M.M.?
   A. Initiate a low-intensity statin
   B. Initiate a moderate-intensity statin
   C. Initiate a high-intensity statin
   D. Initiate a high-intensity statin plus ezetimibe

9. According to the ACC/AHA blood cholesterol guidelines, which is best described as a high-intensity statin dose?
   A. Pravastatin 20 mg/day.
   B. Lovastatin 20 mg/day.
   C. Atorvastatin 40 mg/day.
   D. Rosuvastatin 10 mg/day.

10. Which best describes a potential secondary cause of high TG concentrations?
    A. Amiodarone.
    B. Biliary obstruction.
    C. Sirolimus.
    D. Saturated fats.

V. CHRONIC CORONARY HEART DISEASE AND CHRONIC STABLE ANGINA

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

Depending on the patient’s manifestations, some therapies may be added or modified. However, several basic treatment rules apply to all individuals with CHD, regardless of the symptoms they may experience.
The following mnemonic, developed for patients with chronic stable angina, can be applied to all patients with CHD.

A = Aspirin and antianginal therapy
B = β-Blocker and BP
C = Cigarette smoking and cholesterol
D = Diet and DM
E = Education and exercise

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

Some important recommendations:

- Weight reduction and maintenance to a body mass index of 18.5–24.9 kg/m² and a waist circumference less than 40 inches for male patients and less than 35 inches for female patients
- Physical activity for 30–60 minutes/day, 7 days/week (minimum of 5 days/week)
- BP less than 140/90 mm Hg
- Alcohol consumption should be limited to 1 drink (120 mL [4 ounces] of wine, 360 mL [12 ounces] of beer, or 30 mL [1 ounce] of spirits) per day for women and 1 or 2 drinks per day for men.
- No smoking and no environmental exposure to smoke
- Reduced intake of saturated fats (to less than 7% of total calories), trans fatty acids (to less than 1% of total calories), and cholesterol (to less than 200 mg/day)
- If a patient has DM, A1C less than 7%; a goal A1C of 7%–9% is reasonable in certain patients according to age, history of hypoglycemia, presence of microvascular or macrovascular complications, or comorbid conditions.
- Annual influenza vaccine

Patient Case

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

Therapeutic Management of CHD

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

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

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Aspirin</th>
<th>P2Y12 Inhibitors</th>
<th>Alternative Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIHD treated with PCI and BMS placed</td>
<td>Initial Dose</td>
<td>Subsequent Doses (Starting Day 2) and Therapy Duration</td>
<td>Recommended Minimum Treatment Duration (Class I&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td></td>
<td>325 mg before PCI</td>
<td>75–100 mg/day indefinitely</td>
<td>Clopidogrel for 1 month</td>
</tr>
<tr>
<td>SIHD treated with PCI and DES placed</td>
<td>325 mg before PCI</td>
<td>75–100 mg/day indefinitely</td>
<td>Clopidogrel for 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reasonable to discontinue clopidogrel after 3 months in those at high risk of bleeding or those who experience significant overt bleeding&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reasonable to extend clopidogrel for &gt; 6 mo for those at low risk of bleeding&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

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

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

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

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


C. Lipid-lowering therapy (see section IV: Dyslipidemia)

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

D. ACE Inhibitors

1. Greatly decrease CV events in patients with CHD (and no left ventricular dysfunction) at high risk of subsequent CV events.
2. Should be considered in all patients who also have an LVEF of 40% or less, HTN, DM, and/or CKD (class I recommendation)
3. Consider using in lower-risk patients with a mildly reduced or normal LVEF in whom CV risk factors are well controlled and revascularization has been performed (class IIb recommendation).

E. ARBs: Recommended as an alternative to ACE inhibitors in patients who also have an LVEF of 40% or less, HTN, DM, or CKD or who are unable to tolerate an ACE inhibitor (e.g., cough or angioedema; class IIa recommendation)
F. Additional therapies for chronic stable angina

1. Definition: Predictable angina symptoms with exertion

2. Goals: Reduce symptoms of ischemia, increase physical function, and improve quality of life. In general, achieved by either decreasing myocardial oxygen demand or increasing myocardial oxygen supply

3. Specific agents
   a. β-Blockers
      i. Pharmacologic effects: Decreased inotropy and HR (decrease oxygen demand)
      ii. Goal resting HR 55–60 beats/minute (less than 50 beats/minute if angina symptoms continue)
      iii. Goal exercise HR of no more than 75% HR associated with angina symptoms
      iv. Place in therapy: May be considered chronic therapy for all patients with coronary or other vascular disease. Should be prescribed first-line for relief of angina symptoms in patients with stable ischemic heart disease (class I). Also a class I indication for first 3 years post-MI
      v. Contraindications: Severe bradycardia (HR less than 50 beats/minute), high-degree AV block or sick sinus syndrome (in absence of a pacemaker)

   b. CCBs
      i. Pharmacologic effects
         (a) Decrease coronary vascular resistance and increase coronary blood flow (increase oxygen supply)
         (b) Negative inotropy, to varying degrees; nifedipine much greater than amlodipine and felodipine (decrease oxygen demand)
         (c) Decrease HR (verapamil and diltiazem only; decrease oxygen demand)
      ii. Place in therapy
         (a) Non-DHP CCBs may be added to β-blocker therapy to achieve HR goals (caution advised; combination can cause heart block).
         (b) Instead of β-blocker therapy when unacceptable adverse effects emerge or if treating Prinzmetal’s angina
         (c) Short-acting CCBs (nifedipine) have been associated with increased CV events; should be avoided (except in slow-release formulations)
      iii. Contraindications for non-DHP CCBs: HFrEF, severe bradycardia, high-degree AV block or sick sinus syndrome (in absence of a pacemaker)
      iv. Contraindications for DHP CCBs: HFrEF (except amlodipine and felodipine)

   c. Nitrates
      i. Pharmacologic effects:
         (a) Endothelium-dependent vasodilation, dilates epicardial arteries and collateral vessels (increase oxygen supply)
         (b) Decreased left ventricular volume because of decreased preload mediated by venodilation (decrease oxygen demand)
      ii. Place in therapy
         (a) A scheduled long-acting nitrate is useful in conjunction with a β-blocker or non-DHP CCB, or both (to blunt the reflex sympathetic tone with nitrate therapy).
         (b) As-needed sublingual tablets, powder, or spray nitroglycerin is necessary to relieve effort or rest angina.
         (c) In addition, as-needed sublingual tablets, powder, or spray nitroglycerin can be used before exercise to avoid ischemic episodes.
      iii. Caution: Hypertrophic obstructive cardiomyopathy, inferior wall MI, severe aortic valve stenosis, avanafil within 12 hours, sildenafil and vardenafil within 24 hours, tadalafil within 48 hours
d. Ranolazine
   i. Pharmacologic effects
      (a) Inhibits the late phase of the inward Na channel in ischemic myocytes during repolarization, leading to a reduction in intracellular Na concentrations. This reduction in Na concentrations leads to reduced calcium influx, which decreases ventricular tension and myocardial oxygen consumption.
      (b) Increases “oxygen efficiency”

   ii. Place in therapy
       (a) Ideal role is unclear
       (b) Use in combination with β-blockers, CCBs, and/or nitrates when initial management with these drugs is unsuccessful.
       (c) Use when BP or HR is too low to add β-blockers, CCBs, and/or nitrates
       (d) Modest reduction in hemoglobin A1C
       (e) Important points
           (1) No significant effects on HR or BP; thus, bradycardia and hypotension are not of concern
           (2) Dose-related QT interval prolongation
           (3) Metabolized by CYP3A; P-gp substrate
               (A) Avoid in hepatic dysfunction.
               (B) Avoid use with strong CYP3A inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir.
               (C) Avoid use with CYP3A inducers such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, or St. John’s wort.
               (D) Limit the dose to 500 mg twice daily in patients receiving moderate CYP3A4 inhibitors, including diltiazem, verapamil, erythromycin, fluconazole, and grapefruit juice.

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REFERENCES

Heart Failure


Atrial Fibrillation


Hypertension


Dyslipidemia


CHD and Chronic Stable Angina


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A
This patient has NYHA class III HFrEF with an LVEF of 20%. The best option is to increase her carvedilol dose to the goal dose of 25 mg twice daily (Answer A). Despite her HR of 68 beats/minute, it is safe to increase the β-blocker. Higher carvedilol doses have been associated with reductions in mortality. Appropriate monitoring would include signs and symptoms of hypotension and bradycardia. Her ACE inhibitor is already at the maximum recommended lisinopril dose for heart failure; therefore, further increases are not warranted (Answer B). Spironolactone 25 mg/day is the recommended dose for patients with HFrEF who are already receiving an ACE inhibitor and a β-blocker and are NYHA class III. Increasing the spironolactone dose to 50 mg/day is unwarranted (Answer C). Her digoxin concentration of 0.7 ng/dL is within the desired range of 0.5–0.9 ng/mL; therefore, no dose increase is warranted, because this would not improve efficacy and would only increase the risk of toxicity (Answer D).

2. Answer: B
Increasing the ACE inhibitor to target doses should be achieved in all patients, if possible. This patient’s BP of 120/70 mm Hg safely permits increasing enalapril from 5 to 10 mg twice daily, making Answer B correct. The patient’s SCr does not prevent the enalapril dose from being titrated because it is stable, and he does not have hyperkalemia. There is no consensus that carvedilol is preferred to extended-release metoprolol for patients with HFrEF (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 therapy with an ACE inhibitor, β-blocker, and diuretic. Additionally, digoxin 0.125 mg daily would likely be too high for a patient with a SCr of 2.8 mg/dL. This patient’s ACE inhibitor therapy is not considered optimal (Answer D).

3. Answer: C
Cilostazol, a phosphodiesterase type 3 inhibitor, may be associated with an elevated risk of ventricular arrhythmias and death in patients with HFrEF (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 metoprol tartrate therapy; therefore, no additional AV nodal blockade is warranted with either a non-dihydropyridine CCB (Answer B) or digoxin (Answer A). This patient with AF would be considered at high risk of a stroke because of his history of HTN and TIA. Given these risk factors, this patient has a CHA2DS2-VASc score of 3; therefore, anticoagulation with an oral anticoagulant agent is indicated. Warfarin titrated to a goal INR of 2.5 would be a potentially appropriate option; however, this patient may be unable to travel to his primary care provider’s office for weekly INR checks (Answer C). In this case, dabigatran 150 mg twice daily (Answer D) may be the best choice because it does not warrant INR monitoring, the patient has prescription insurance, he appears to be adherent to a twice-daily medication regimen already, and he does not have renal impairment.

5. Answer: C
With the new diagnosis of HFrEF, this patient can no longer receive sotalol. Discontinuing this medication is important so that his risk of arrhythmic death is not increased. Adding metoprolol is a reasonable approach, but not until his HF has been properly controlled, making both Answers A and D incorrect. If rhythm control is desired, amiodarone and dofetilide are the only two antiarrhythmic drugs that have been proved safe and effective in patients with HFrEF, making Answer C correct. Of importance, drug interactions exist between amiodarone, digoxin, and warfarin, which will need to be addressed. Dronedaron (Answer B) is not recommended in patients with symptomatic HF with a recent decompensation.
6. **Answer: B**  
W.D.’s blood pressure falls into the stage 2 HTN category. The ACC/AHA guidelines recommend two-drug therapy for patients with stage 2 HTN, making answers A and D incorrect. This patient recently suffered from a myocardial infarction, and the ACC/AHA guidelines recommend both β-blockers and ACE inhibitors or ARBs for treatment of HTN in ischemic heart disease, making answer B correct. Answer C would be an appropriate alternative regimen if the patient were African American, but W.D. is white.

7. **Answer: B**  
T.J.’s blood pressure falls into the stage 1 HTN category. Patients with stage 1 HTN should receive pharmacologic treatment in addition to lifestyle modifications, making answer A incorrect. Patients with stage 1 HTN should be started on a single drug regimen, making answer D incorrect. According to the ACC/AHA guidelines, patients with diabetes can be initiated on ACE inhibitors, ARBs, thiazide diuretics, or calcium channel blockers. However, because this patient is African American and she does not have albuminuria, her initial HTN regimen should include a calcium channel blocker or a thiazide diuretic because these agents are more effective at lowering BP than ACE inhibitors and ARBs. Therefore, answer C is incorrect and answer B is the best choice.

8. **Answer: C**  
This patient falls into the patient management group of patients with diabetes and age 40-75 years. Because she has multiple ASCVD risk factors including smoking, low HDL-C, and HTN, this patient would benefit from high-intensity statin therapy (answer C). Answer B would be correct if M.M. did not have additional ASCVD risk factors. Low-intensity statins are not recommended for initial therapy for any patient in the 2018 ACC/AHA Cholesterol guidelines (answer A). This patient should receive maximally tolerated statin therapy and be assessed for response before the addition of ezetimibe (Answer D).

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

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

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

1. Answer: D
This patient has HFrEF (NYHA class III), probably secondary to her MI 4 months ago, and is not receiving optimal HF therapy with an ACE inhibitor and β-blocker, making Answer A incorrect. ACE inhibitors are considered the cornerstone of therapy for HFrEF because evidence shows that they slow the progression of HF and reduce symptoms, hospitalizations, and mortality in this patient population. ACE inhibitors should be initiated in all patients with HFrEF, unless there is a contraindication. This patient has no contraindications for using an ACE inhibitor; therefore, lisinopril should be initiated (Answer D). Digoxin is not indicated unless a patient is symptomatic on optimal HF therapy (Answer B). This patient is not symptomatic and is not receiving optimal therapy. Although the patient is NYHA class III, no rationale exists for adding spironolactone at this time because she is not receiving optimal HF therapy (Answer C).

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

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

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

5. Answer: A
This patient is experiencing a rapid ventricular response with exercise or strenuous activity, causing the sensation of palpitations and dyspnea. Digoxin alone poorly controls the ventricular rate during times of high sympathetic influence (e.g., exercise). Additional therapy is usually necessary to control the ventricular rate adequately. A β-blocker such as metoprolol succinate is a good choice to maintain HR during activity (Answer A). Using verapamil with digoxin in this patient could result in signs or symptoms of toxicity, given his current digoxin concentration. In addition, he is already taking a CCB, making verapamil a bad choice (Answer
D). Similarly, doubling the digoxin dose would almost double the current serum concentration to 2.2 ng/dL, which should be avoided (Answer B). Instructing the patient to avoid activity is undesirable because physical activity should be encouraged and supported in all patients, especially in those with risk factors for CV disease (Answer C).

6. Answer: A
According to the ACC/AHA guidelines, this patient’s BP goal is less than 130/80 mm Hg because he has no clinical CVD and a 10-year ASCVD risk ≥10%, making answers B and D incorrect. Beta blockers are not recommended first-line for HTN management in the absence of coronary artery disease, heart failure, or atrial fibrillation, making answer C incorrect. Answer A includes a first-line HTN medication which also maintains efficacy in the African American population.

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 patient management groups (age 40–75 years with an LDL-C of 70–189 mg/dL and a 10-year ASCVD risk of 7.5-19.9% without DM or ASCVD) and thus should be initiated on statin therapy. According to the guidelines, this patient should be treated with moderate- to high-intensity statin therapy. Although simvastatin 20 mg is considered a moderate-intensity dose, adding gemfibrozil to this patient’s regimen would be inappropriate because gemfibrozil is contraindicated in combination with simvastatin; also, his TG concentrations are less than 500 mg/dL and need not be specifically targeted (Answer A). Using pravastatin 20 mg would be inappropriate because this is considered a low-intensity dose, and it would not provide the more than 30%-50% reduction in LDL-C that is recommended. In addition, fenofibrate would not be needed because his TG concentrations are lower than 500 mg/dL (Answer C). Rosuvastatin 2.5 mg is a low-intensity dose and would not be appropriate (Answer B). Atorvastatin 20 mg is considered a moderate-intensity dose, and it will provide a 30%-50% reduction in LDL-C, as is recommended (Answer D).

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

9. Answer: D
Secondary causes of hypertriglyceridemia should be ruled out when TG concentrations are greater than 500 mg/dL or when LDL-C is greater than 190 mg/dL. Different medications, conditions, and diet can affect these lipid values. Although obesity, poorly controlled DM, olanzapine, and metoprolol can increase TG concentrations, coenzyme Q does not affect TG; therefore, Answer A is incorrect. Alcohol consumption, poorly controlled DM, and β-blockers can all increase TG, but weight loss does not increase TG. Weight loss can actually lower LDL-C and TG; therefore, Answer B is incorrect. All the choices in Answer C can increase TG, making Answer C incorrect. All the conditions, medications, or disease states in Answer D can increase TG, making this option correct.

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

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

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