Overview of Hyperlipidemia and Hypertension

LEARNING OBJECTIVES

Upon completion of this module, the subscriber will be able to:

1. Recognize the risk factors associated with the development of hyperlipidemia and hypertension.
2. Describe the role of cholesterol in the development of atherosclerosis and the long-term consequences of uncontrolled hypertension.
3. Identify the appropriate treatment goals when managing hyperlipidemia and hypertension.
4. Recognize the names, mechanisms of action, doses, and side effects of the drugs used in the treatment of hyperlipidemia and hypertension.
5. Recall the specific patient populations that may require additional or different drug treatment and treatment goals than the general population in the management of hyperlipidemia and hypertension.

ACCREDITATION

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This module will provide 2.5 contact hours of continuing pharmacy education credit for pharmacy technicians.

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Overview of Hyperlipidemia and Hypertension

Overview
Cardiovascular disease (CVD) is a broad term that includes high blood pressure, heart attack, chest pain, heart failure, and stroke. Current estimates are that 85.6 million American adults have 1 or more types of CVD and about 50% are 60 years of age or older. CVD continues to be the number 1 cause of death in the United States (US) accounting for about 1 of every 3 deaths or 1 death every 40 seconds. The good news is that from 2003 to 2013, the death rate from CVD declined by 28.8%. As an effort to continue this trend in decreasing CVD mortality, the American Heart Association (AHA) has expanded its focus to include CVD prevention in addition to treatment. The AHA defines cardiovascular health by 7 metrics, referred to as "Life's Simple 7". These metrics are a combination of lifestyle and health factors. Ideal cardiovascular health is defined as optimal levels of all 7 metrics: heart healthy diet, adequate physical activity, not smoking, and maintaining normal body weight, blood pressure, cholesterol, and glucose levels. The more risk factors that are optimally controlled the lower the risk of CVD death.

This module will focus on prevention and treatment of high cholesterol levels (hyperlipidemia) and high blood pressure (hypertension) as a mechanism to decrease cardiovascular risk.

Hyperlipidemia

Introduction to Hyperlipidemia

What is it and Who is Affected?

Hyperlipidemia is a condition characterized by elevated levels of fats or lipids in the blood. The term “lipids” generally refers to cholesterol and triglycerides which are found in the blood. An elevation in low density lipoproteins (LDL), one of the three main subclasses of cholesterol, has been linked to the development of atherosclerosis and coronary heart disease (CHD). Atherosclerosis is a disease in which plaque builds up inside the artery wall and overtime leads to hardening and narrowing of the arteries. A LDL cholesterol level greater than 100 mg/dL is associated with the development of atherosclerosis. Heart disease is the leading cause of death in the US, and CHD is the most common type of heart disease. CHD caused about 1 of every 6 deaths in the US in 2010. Approximately every 34 seconds, one American adult has a coronary event, and approximately every minute an American adult will die of one. Heart disease also places a financial burden on society with the total direct and indirect cost of CVD in 2010 estimated to be $315.4 billion. For comparison, the estimated cost of all cancers was $201.5 billion. CVD costs more than any other disease state.

Who is at Risk for CHD?

A number of factors are associated with increased risk of CHD. While some risk factors are called “modifiable” or are able to be treated through pharmacological (medications) or lifestyle management, others are “non-modifiable” or are fixed and unchangeable. The presence of “non-modifiable” risk factors may signal the need for more intense pharmacologic therapy (Table 1).

Modifiable Risk Factors

All patients with risk factors should aim to reduce these in order to decrease the chances of developing CHD. Examples of risk reduction include smoking cessation, treatment and control of hypertension and diabetes, weight reduction, increased physical activity, and improvement in diet.

Table 1. Risk Factors for Coronary Heart Disease

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Non-Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Age</td>
</tr>
<tr>
<td>Cigarette Smoking</td>
<td>Male Sex</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Family History of Premature Coronary Heart Disease</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Physical Inactivity</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td></td>
</tr>
</tbody>
</table>
Hypertension
Hypertension, will be discussed in greater detail in the second part of this module. Elevated blood pressure can damage walls of arteries over time and this damage causes an increase in the accumulation of cholesterol, platelets, and fats. Additionally, arteries may have acceleration in their rate of hardening. Multiple studies have shown a strong association of high blood pressure with risk for CHD and these two conditions often occur together.2

Cigarette Smoking
Cigarette smoking is known to be a strong contributor for increased risk of CHD, and data suggest that smoking cessation reduces the risk for CVD events within months after quitting.2 Various trials have shown that people who quit smoking have a significant decrease in the risk for cardiovascular events. Smoking is a factor used in risk-assessment tools because people who smoke often benefit more from reduction in LDL than nonsmokers. Risk-assessment tools will be discussed in the section titled, “Recent Guideline Updates and Shift in Practice.”

Diabetes
Diabetes, defined as fasting (not eating for 9 to 12 hours) blood glucose of 126 or greater (confirmed with repeat testing), increases risk for all forms of CVD including CHD in both patients with type 1 and type 2 diabetes mellitus.2 It has been shown that the death rate in patients with diabetes and CHD is also higher. An improvement in glucose control and other modifiable risk factors has been definitively linked to a decrease in CHD. There is a very high burden of illness and mortality associated with the development of CHD in patients with diabetes.2

Obesity
It is estimated that more than one-third of all adults in the US are obese with non-Hispanic blacks having the highest age-adjusted rates followed by Hispanics.5 Obesity is higher among middle-aged adults, 40-59 years old. The Centers for Disease Control and Prevention (CDC) defines obesity as a Body Mass Index (BMI) higher than 30 and overweight as a BMI between 25.0 and 29.9. Being overweight or obese has been linked to an increased risk of developing CVD, hypertension, stroke, diabetes and even greater death rate with the presence of multiple risk factors. Risk for CVD is primarily raised when abdominal obesity, defined by a waist circumference greater than 40 inches in men or 35 inches in women.2 Weight loss is associated with a decrease in cholesterol levels.6

Physical Inactivity
Physical inactivity is also associated with increased risk for CHD and an increase in the amount of physical activity has been found to favorably affect all lipid levels such as decreasing LDL cholesterol, increasing high density lipoprotein (HDL) or “good” cholesterol, and decreasing triglycerides.2 Although the full mechanism connecting physical inactivity to CHD has not been fully identified, lack of physical activity likely contributes to obesity and associated risk factors.

Diet High in Saturated Fats
Multiple dietary factors influence blood lipid levels. Diets high in trans fats, saturated fats, and dietary cholesterol are associated with elevated cholesterol levels as well as increasing risk for other established risk factors.7 Foods high in trans and saturated fats include: deep-fried food, margarine, shortening, cake frosting, creamer, store-bought cookies and cakes, and creamy frozen drinks. It is not uncommon for some people to have little change in lipid values despite significant changes in fat and cholesterol intake, which can likely be explained by non-modifiable risk factors such as genetics.

Non-Modifiable Risk Factors
Age
Risk for CHD increases significantly with increases in age of both men and women.2 At any level of LDL cholesterol, the risk for CHD is higher in older people than younger people. The theory behind this finding is that with increasing age there is an increased amount of atherosclerosis which may form a plaque and is a reflection of a higher total exposure to other risk factors.

Male Sex
At any given age, men are at a higher risk of CHD than women. In general, the risk for women lags about 10 to 15 years behind men’s risk.2 The reasons for this have not been identified; however treatment of women with LDL-lowering therapy correlates to a similar risk reduction in men.
Family History of Premature CHD

Several studies have determined that family history of premature CHD is another significant risk factor, because it has a strong association with the development of CHD. The risk increases with younger ages of onset and with the number of first-degree relatives affected. A positive family history includes any first-degree relative such as a parent, sibling, or child.

Pathogenesis and Diagnosis

Introduction

Cholesterol and triglycerides are the major blood lipids and are essential for the formation of cell membranes, hormone production and provide an energy source in the form of free fatty acids. Because lipids are not water soluble, they do not circulate in the blood in free form but rather bound to proteins in a macromolecule called a lipoprotein.

Classification of Lipoproteins by Density

The density of lipoproteins is determined by their content of protein and lipid (Table 2). LDL carries 60% to 70% of the total blood cholesterol. High-density lipoprotein (HDL) carries about 20% to 30% of total blood cholesterol. Very-low-density lipoprotein (VLDL) carries about 10% to 15% of total blood cholesterol and most of the triglycerides in a fasting state.

<table>
<thead>
<tr>
<th>Lipoprotein Class</th>
<th>Density (g/mL)</th>
<th>Diameter (nm)</th>
<th>Protein</th>
<th>Triglyceride</th>
<th>Phospholipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>&lt; 0.94</td>
<td>75-1200</td>
<td>1-2</td>
<td>80-95</td>
<td>3-9</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.94-1.006</td>
<td>30-80</td>
<td>6-10</td>
<td>55-80</td>
<td>10-20</td>
</tr>
<tr>
<td>LDL</td>
<td>1.006-1.063</td>
<td>18-25</td>
<td>18-22</td>
<td>5-15</td>
<td>18-24</td>
</tr>
<tr>
<td>HDL</td>
<td>1.063-1.21</td>
<td>5-12</td>
<td>45-55</td>
<td>5-10</td>
<td>20-30</td>
</tr>
</tbody>
</table>

VLDL = very-low-density lipoprotein
LDL = low-density lipoprotein
HDL = high-density lipoprotein
< = less than
high-energy expenditure. Chylomicrons are normally not present in the blood in a fasting state.8

**Endogenous Pathway**

The liver is primarily responsible for the regulation of cholesterol in the body. The endogenous pathway begins in the liver with the creation of VLDLs.8 VLDL production is stimulated in the liver when there is an increase in the number of free fatty acids. An enzyme breaks down VLDLs into IDLs. The liver either removes IDLs or they are further processed into cholesterol-rich LDLs. LDL particles last longer in the circulation than VLDLs and contain about two-thirds of all blood cholesterol.10 Lastly, LDLs are recycled back into the liver or other peripheral cells via LDL receptors. This process is ultimately regulated by cellular cholesterol requirements. When fasting or on low-fat intake, most cholesterol is created in organs other than the liver.8 Of note, the rate-limiting enzyme for intracellular creation of cholesterol is 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the target of drug class known as the statins such as simvastatin or atorvastatin. A person’s genetics may create abnormalities in the gene that destroys LDL receptors, proprotein convertase subtilisin-kexin type 9 (PCSK9). This abnormality can cause blood elevations in LDL by increasing the destruction of LDL receptors and decreasing the uptake of LDL into the liver. Lastly, LDL may be excreted into stomach fluid and excreted out of the body through the stool.

HDL has been linked to removing extra VLDL or LDL from the blood and brought back to the liver or to the bile for elimination. This process accounts for some of the beneficial effects noted with HDL, sometimes referred to as the “good cholesterol.”

**What is the Link Between Cholesterol and Atherosclerosis?**

Atherosclerosis means thickening, narrowing and hardening of the arteries caused by a build-up of plaque. The underlying pathophysiology is explained by a chronic inflammatory state causing dysfunction of the arterial wall and an increase in the accumulation of LDL particles.11 When LDL particles adhere to the vessel they are susceptible to a chemical reaction called, “oxidation”. Oxidized lipids and LDL increase inflammation of the artery that causes further cell infiltration by LDL particles. Eventually a plaque forms and can become covered in a fibrous cap containing colla-
gen and smooth muscle cells. Over time and with increased growth the plaque can be prone to rupture. The body tries to heal this rupture by forming a blood clot (or thrombus), but the clot blocks off blood flow within the artery and oxygen delivery beyond the clot. This plaque rupturing and thrombus formation can result in either a heart attack or stroke. The pathogenesis of atherosclerosis is very complex and is an active area of research.

**How is Hyperlipidemia Diagnosed?**

Levels of cholesterol and triglycerides are evaluated with a blood test called a “lipid panel” or “lipid profile.” The sample can be obtained via a blood draw or point-of-care finger stick methods. This lab test reports total cholesterol, LDL-C, HDL-C, and triglycerides and is best performed in a fasting state (i.e. 9 to 12 hours) to eliminate interference of any dietary fat or dietary cholesterol in the result. LDL is typically a calculated value based on the measurement of total cholesterol, total triglycerides, and HDL.

\[
LDL-C = TC - HDL-C - TG/5
\]

\[
(LDL-Cholesterol) = (Total Cholesterol) - (HDL Cholesterol) - (Triglycerides divided by 5)
\]

The above equation is not accurate for persons with triglycerides greater than 400 mg/dL, and a more complex, specialized laboratory technique is required for accuracy. A fasting lipid panel should be measured in all adults 20 years of age or older at least once every 5 years.

**Test Your Knowledge #2**

1. Using the LDL-C equation above, calculate the LDL-C in someone with a total cholesterol (TC) of 200 mg/dL, HDL of 60 mg/dL, and triglycerides of 125 mg/dL.

2. According to the “Classification of Cholesterol Levels” table (Table 3), how would you classify this cholesterol level?

Answers on page 36.

**Table 3. Classification of Cholesterol Levels**

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>LDL Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200 mg/dL</td>
<td>Optimal</td>
</tr>
<tr>
<td>200-239 mg/dL</td>
<td>Above Optimal</td>
</tr>
<tr>
<td>≥ 240 mg/dL</td>
<td>Borderline High</td>
</tr>
<tr>
<td>130-159 mg/dL</td>
<td>Borderline High</td>
</tr>
<tr>
<td>160-189 mg/dL</td>
<td>High</td>
</tr>
<tr>
<td>≥ 190 mg/dL</td>
<td>Very High</td>
</tr>
<tr>
<td>&lt; = less than</td>
<td></td>
</tr>
<tr>
<td>≥ = greater than or equal to</td>
<td></td>
</tr>
</tbody>
</table>

**Recent Guideline Updates and Shift in Practice**

National Heart, Lung, and Blood Institute (NHLBI) guideline on high blood cholesterol in adults (National Cholesterol Education Program Adult Treatment Panel III, ATP III) Classification of cholesterol levels can be found in Table 3. This guideline was published in 2002 and emphasized treating patients to a certain goal LDL value that varied depending on concurrent diseases or risk factors. LDL goals could range anywhere from less than 160 mg/dL for a person with the lowest risk to less than 70 mg/dL in a person with a very high risk. In 2013, the American College of Cardiology (ACC) and AHA released new guidelines for the treatment of cholesterol that de-emphasizes numerical targets for LDL cholesterol and instead focuses on targeting treatment to patients who are at an increased risk for atherosclerotic cardiovascular disease (ASCVD). The guideline is intended for use in adults who are 21 years of age or older. In addition to assessing blood cholesterol levels, the factors assessed include age, gender, race, smoking status, blood pressure and whether it is being treated, and diabetes status. This way of practice shifts thinking away from targeting blood cholesterol levels to treating based on an overall risk. Based on this recommendation it is believed that about one third of adults in the US could benefit from a class of cholesterol lowering medications called statins.
Table 4. Intensity of Statin Therapy\(^\text{12}\)

<table>
<thead>
<tr>
<th>STATIN</th>
<th>HIGH</th>
<th>MODERATE</th>
<th>LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin (Lipitor)</td>
<td>40-80 mg</td>
<td>10-20 mg</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin (Lescol)</td>
<td>40 mg (twice a day)</td>
<td>20-40 mg</td>
<td></td>
</tr>
<tr>
<td>Lovastatin (Mevacor)</td>
<td>40 mg</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin (Livalo)</td>
<td>2-4 mg</td>
<td>1 mg</td>
<td></td>
</tr>
<tr>
<td>Pravastatin (Pravachol)</td>
<td>40-80 mg</td>
<td>10-20 mg</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin (Crestor)</td>
<td>20-40 mg</td>
<td>5-10 mg</td>
<td></td>
</tr>
<tr>
<td>Simvastatin (Zocor)</td>
<td>20-40 mg</td>
<td>10 mg</td>
<td></td>
</tr>
</tbody>
</table>


ASCVD = atherosclerotic cardiovascular disease
Clinical ASCVD = acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or atherosclerotic peripheral arterial disease
> = greater than
≥ = greater than or equal to
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in non-Hispanic Caucasian and African American women and men aged 40 to 79 years with or without diabetes who have a LDL-C level between 70 and 189 mg/dL. Individuals who are not on any cholesterol-lowering therapy should have their ASCVD risk calculated every 4 to 6 years. Under the old ATP III guidelines calculated risk only accounted for heart disease, but the new risk assessment calculator also adds the risk of stroke. Some patients may not fall into the four categories but may still benefit from statins, and a patient and their health-care provider may make a decision to treat the patient based on other clinical factors that the guideline does not account for. Other organizations provide commentary on cholesterol management as well, and not all recommendations are in agreement. However, for the sake of this program, the focus will remain on guidelines from ACC/AHA.

Treatment

Non-Pharmacologic (Non-Medication) Therapy

The backbone of treating hyperlipidemia is lifestyle changes.\textsuperscript{8,12} This includes dietary therapy that has low intake of total fat, saturated fat and cholesterol. If necessary a registered dietitian may be consulted to help patients change their diet. In addition to making healthy food choices, patients must be encouraged to exercise. A reasonable goal is at least 30 minutes of moderate-intensity exercise at least 5 days a week. All patients should be encouraged to use diet and exercise as a way to maintain healthy weight, limiting alcohol use and avoiding tobacco use.

Pharmacologic (Medication) Therapy

Lipid-modifying drug therapy has been shown to slow the advancement of atherosclerotic disease, stabilize atherosclerotic plaques, and improve cardiovascular outcomes.\textsuperscript{14} Drug treatment should be considered in addition to diet and lifestyle changes. A heart healthy diet and lifestyle modifications were recommended in addition to cholesterol-lowering therapies in all the trials that evaluated these drugs.\textsuperscript{12} There are seven drug classes used to treat hyperlipidemias. They all differ in their mechanisms of action, impact on lipid levels, drug interactions, contraindications, and side effects.

2013 Guideline ACC/AHA Recommendations on Therapy Selection

These guidelines overwhelmingly support the use of statins as first-line for prevention of ASCVD based on available evidence from trials showing a decreased incidence of CHD and death.\textsuperscript{12} To determine the dose or statin intensity, the guideline provides an algorithm that determines: 1) which groups of patients would benefit from statin therapy and 2) the intensity of statin therapy that is indicated (Figure 2, Table 4). The guidelines do not support the use of non-statin drug therapy in addition to statins based on a lack of supporting data. Non-statin therapies may be considered in patients who are completely statin-intolerant or high-risk patients who do not respond to statin therapy or who cannot tolerate the recommended intensity of statin therapy. High risk patients are defined by the presence of clinical ASCVD, with a LDL-C of 190 mg/dL or greater, and individuals with diabetes.

Statins

As mentioned previously in the “Where Does Cholesterol Come From” section of this module, statins are HMG-CoA reductase inhibitors, meaning they inhibit the rate-limiting step of cholesterol production in the liver.\textsuperscript{14} Due to a decreased production of cholesterol in the liver, the liver up-regulates its production of LDL receptors that ultimately increases LDL clearance from the circulation. Statins are prescribed primarily for their LDL lowering capabilities but can also lower triglycerides and raise HDL. There are seven different types of statins (Table 5, page 10). They all differ in their LDL-lowering efficacy and potential for drug and disease interactions based on their metabolic fates. All statins are classified as category X in pregnancy and should be used cautiously in women of childbearing potential. Drugs that are classified as category X are those that are known to cause fetal birth defects when taken by pregnant mothers.

Intensity of Statin Therapy

Statin drugs are classified as low, moderate, or high intensity based on how much they lower the LDL level in the blood.\textsuperscript{12} On average, high-intensity statin therapy lowers LDL-C on average by over 50%, moderate-intensity statin therapy lowers LDL-C by 30% to 50%, and low-intensity statin therapy lowers LDL-C by less than 30% (Table 4).
### Side Effects

**Muscle Side Effects**

In general, statins are better tolerated compared to other classes of lipid-modifying drugs. The most common side-effect is muscle toxicity. The mechanism by which statins cause muscle toxicity is not well-understood. There are specific definitions for the different types of statin-associated muscle adverse events defined by the National Lipid Association’s Muscle Safety Expert Panel (Figure 3). Myalgia is defined as unexplained muscle discomfort with normal creatine kinase (CK), an enzyme found in skeletal muscle cells. Myopathy is defined as muscle weakness not associated with pain or CK elevations. Myonecrosis is defined by an elevation in CK. Myonecrosis with acute renal failure is defined as rhabdomyolysis. Myalgias or myopathies are less severe and are reported in about 5% of patients. Rhabdomyolysis is life-threatening and is reported in less than 1% of patients.

It is important to distinguish which muscle toxicity a patient is experiencing in order to treat it appropriately. The ability to cause muscle toxicity varies among the statins. The risk is lowest with pravastatin and rosvastatin. This is because they are attracted to water (i.e. hydrophilic) and may have less penetration into muscle than statins that are chemically more attracted to fats (i.e. lipophilic) (Table 5). Other risk factors for muscle toxicity include pre-existing muscle disorders, hypothyroidism, genetic factors, and concurrent drug therapy, specifically those drugs that inhibit drug break down by the liver. Simvastatin, lovastatin, and atorvastatin are broken down in the liver and drugs that inhibit this process increase the risk of statin myopathy. The simvastatin package insert has specific labeling with recommendations for dosing limitations when simvastatin is used concomitantly with other drugs due to an increased risk of muscle toxicity. The simvastatin dose cannot exceed 10 mg in patients on verapamil (Calan, Verelan), diltiazem (Cardizem, Tiazac, Cartia, Diltzac, etc.) or dronedarone (Multaq); and 20 mg in patients on amiodarone (Cordarone, Pacerone), amlo-dipine (Norvasc), or ranolazine (Ranexa). The diagnosis of muscle toxicity is made by assessing symptoms and timing to when the statin was started; and other possible causes (e.g. whether there is another reason the patient may have muscle pain such as recent exercise or muscle exertion), and analyzing blood CK levels that may or may not be elevated. Patients who have severe muscle toxicity should discontinue therapy and the symptoms should resolve with statin withdrawal. Re-trial of statin therapy with a different statin, a lower dose and/or decreased dosing frequency may be appropriate depending on the clinical scenario.

### Liver Side Effects

Abnormal values in blood tests of the liver are reported in up to 3% of patients taking statins. These elevations are primarily related to the dose and occur during the first three months of therapy. Severe liver toxicity is rare.

### Safety and Monitoring

A follow-up lipid blood test 4 to 12 weeks after starting therapy or after a change in the dose of a statin is recommended to make sure the patient is taking the medication correctly and the LDL levels are decreasing as expected based on the intensity of statin being used. Routine monitoring of CK is not recommended but it may be useful to obtain a baseline CK as a reference if any muscle toxicity occurs in the future. Statins should be discontinued in patients with CK elevations greater than 10 times the upper limit of normal (ULN) and no muscle symptoms or CK elevations of greater than 3 times the ULN and with muscle symptoms. Similar recommendations are made.

| Table 5. Properties of Statins[
<table>
<thead>
<tr>
<th>STATIN</th>
<th>Dose Range</th>
<th>% LDL Lowering</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin (Lipitor)</td>
<td>10 - 80 mg</td>
<td>38-54</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Fluvastatin (Lescol)</td>
<td>20 - 80 mg</td>
<td>17-33</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Lovastatin (Mevacor)</td>
<td>10 - 80 mg</td>
<td>29-48</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Pitavastatin (Livalo)</td>
<td>1 - 4 mg</td>
<td>31-41</td>
<td>Lipophilic</td>
</tr>
<tr>
<td>Pravastatin (Pravachol)</td>
<td>10 - 80 mg</td>
<td>19-40</td>
<td>Hydrophilic</td>
</tr>
<tr>
<td>Rosuvastatin (Crestor)</td>
<td>5 - 40 mg</td>
<td>52-63</td>
<td>Hydrophilic</td>
</tr>
<tr>
<td>Simvastatin (Zocor)</td>
<td>5 - 80 mg</td>
<td>28-41</td>
<td>Lipophilic</td>
</tr>
</tbody>
</table>
for liver function tests. In the past, routine monitoring of liver function was required for people taking statins but the most recent guidelines suggest repeating one only if there are symptoms of liver toxicity. Statins should be discontinued in patients with elevations in liver function tests that are greater than 3 times the ULN.

**Bile-Acid Sequestrants**

Bile-acid sequestrants (BAS) are also called anion-exchange resins because they bind bile acid through an anion exchange reaction. Normally, bile acids work to emulsify dietary fats in order to help them get absorbed in the small intestine. BAS prevent dietary fat absorption and increase their excretion in the stool. Due to a decreased absorption of bile acids, the liver increases the production of bile acids from blood cholesterol and thus increases removal of cholesterol from the circulation. As a class, their main effect is to decrease LDL levels. There are three BAS available for use: cholestyramine (Questran), colestipol (Colestid), and colesevelam (Welchol). BAS therapy has two key disadvantages: they are inconvenient to administer and have uncomfortable side effects. All three can be administered as powders that must be mixed with water or juice and are taken once or twice daily with meals. Colestipol and colesevelam are also available as tablets. Because BAS site of action is in the intestines, they can decrease the absorption of multiple drugs when administered at the same time. It is generally recommended that co-administration of BAS with other drugs should be separated by one hour before or four hours after other drugs.

**Side Effects**

Since BAS are not absorbed, they lack systemic toxicity. Still, their use is often limited by gastrointestinal side effects including nausea, bloating, constipation, and cramping. Colesevelam has been reported to have better tolerability than the other BAS. Sequestrants cause an increase in blood triglycerides and because of this there are safety concerns.

**Safety and Monitoring**

BAS should not be used in individuals with baseline fasting triglyceride levels of 300 mg/dL or more because severe triglyceride elevations may occur. If baseline triglyceride levels are 250 to 299 mg/dL it is reasonable to obtain a fasting lipid panel in 4 to 6 weeks after initiation. If triglycerides rise to greater than 400 mg/dL BAS therapy should be discontinued.

**Niacin**

Niacin is used to describe both nicotinic acid and nicotinamide, however, only nicotinic acid has lipid lowering properties. Nicotinamide only functions as a vitamin. The mechanism of niacin is not fully understood but it appears to inhibit the production of lipoproteins and decreases production of VLDL in the liver. It also decreases blood concentrations of triglycerides and increases HDL. Among all of the available lipid-lowering agents, it appears niacin has the most favorable effect on the lipid profile. Niacin is available with and without a prescription and is usually inexpensive. The extended-release formulation, Niaspan, requires a prescription. Niacin is typically administered in two to three doses per day except for Niaspan which is taken as a single dose at bedtime. Since some niacin preparations are available over-the-counter it is important to counsel patients that their use is associated with many side-effects, some life-threatening, and requires regular monitoring by a health care professional.
Side Effects
Niacin has multiple side effects that limit its long-term use. The most common side effect is flushing (redness) of the skin often described as a “hot flash.” This often leads to discontinuation of the drug. Most people develop tolerance after prolonged use. To reduce the frequency and severity of these skin reactions, it is important to increase the dose of niacin slowly over a period of weeks. Other strategies include taking niacin with food or premedicating with one dose of aspirin 325mg 30 minutes before administration. Niaspan is associated with less flushing. Niacin is also associated with gastrointestinal symptoms such as nausea, diarrhea, flatulence, vomiting, and peptic ulcer disease. Other side effects include liver toxicity, hyperglycemia (elevated glucose or sugar in the blood), and hyperuricemia (elevated uric acid in the blood). Significant liver toxicity is more common with high doses of the short-acting formulation of niacin.

Safety and Monitoring
All patients starting on niacin therapy should get baseline liver function tests, blood glucose or hemoglobin A1C, and uric acid levels. These should be repeated during up-titration and every 6 months thereafter. Niacin should be discontinued if liver function tests increase greater than 3 times the ULN, the patient has severe skin symptoms, persistent hyperglycemia, acute gout (elevated uric acid), or severe gastrointestinal symptoms or unexplained weight loss, and/or the patient develops new-onset atrial fibrillation (rapid, irregular heart beat).

Fibrates
Fibrates or fibric-acid derivates have a complex mechanism of action and may vary between the drugs in its class. It is thought that fibrates work in the liver to reduce the formation of VLDL triglycerides. Fibrates are primarily used to decrease the level of triglycerides up to 35 to 50% in people with hypertriglyceridemia; and have very modest LDL-lowering effects, however, sometimes, LDL levels rise. Elevated triglycerides increase the risk for pancreatitis (inflammation of the pancreas). There are two fibrates currently on the market: gemfibrozil (Lopid) and fenofibrate (Tricor, Antara, Triglide, Fenoglide). They are administered once daily to twice daily and come in tablet and capsule formulations. Fibrates are highly-bound to blood albumin (which means they may interact with other medications) and can cause displacement of other protein-bound drugs when administered together.

Side Effects
Fibrates are generally well-tolerated but the most common side-effect associated with their use is gastrointestinal complaints. They also increase the risk for the formation of gallstones and may increase the risk of muscle toxicity when given together with statins. Of note, the risk of muscle toxicity is lessened with fenofibrate.

Safety and Monitoring
Since fibrates are primarily broken down in the liver and excreted by the kidneys, their blood levels can be increased in people with kidney disease leading to an increased risk of myopathy and rhabdomyolysis. It is recommended that kidney function testing be completed at baseline, within 3 months of starting therapy, and every 6 months thereafter. Fibrates are contraindicated in patients with severe renal or liver dysfunction and may require dose reduction in patients with mild to moderate renal dysfunction. Gemfibrozil in particular has two drug interactions that are contraindicated to be used together because of an increased risk of myopathy and rhabdomyolysis and severe hypoglycemia: simvastatin (Zocor) and repaglinide (Prandin), respectively. Since fenofibrate has less of an impact on statin metabolism, it is the preferred fibrate to use with statins.

Cholesterol-Absorption Inhibitors
Ezetimibe (Zetia) is the only drug in the class of cholesterol-absorption inhibitors. It works by preventing a particular protein that results in decreased absorption of cholesterol in the gut. This inhibition is only for cholesterol and there is no impact on the absorption of other drugs or fat-soluble vitamins. A decrease in the cholesterol delivery to the liver results in an increase in the uptake of cholesterol in the blood stream by the liver and decreased level of systemic cholesterol. Ezetimibe has modest effects on LDL as well as other cholesterol parameters and because of this is FDA-approved only as an add-on therapy to statins or fibrates. Ezetimibe’s place in therapy is primarily in patients who are high-risk, such as those with a history of prior myocardial infarction or diabetes, and cannot tolerate high-intensity statin therapy and otherwise do not meet cholesterol goals on lower doses alone. Ezetimibe was studied in the IMPROVE-IT trial which showed that it improved cardiac outcomes in patients who had a heart attack in the past. Ezetimibe is administered as a tablet taken once daily.
Side Effects

Ezetimibe is typically well-tolerated and takes on the side effect profile of statins when they are used as combination therapy. Myopathy is rarely reported with ezetimibe used alone.

Safety and Monitoring

Fenofibrate and ezetimibe both increase cholesterol in the bile and may increase the risk of gallstones so closer monitoring should be considered.

PCSK9 Inhibitors

Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are the newest cholesterol lowering drugs to come to market. This new drug class includes two drugs: evolocumab (Repatha) and alirocumab (Praluent). Both drugs are monoclonal antibodies that bind to and inhibit the PCSK9 enzyme responsible for the degradation of LDL receptors in the liver. By increasing LDL receptors in the liver, there is an increase in the removal of cholesterol from the blood stream. This novel mechanism leads to significantly decreased LDL levels (up to 70%), more than any other lipid-lowering therapy currently available. Because of their potent LDL lowering effects their target population is those who have CVD and need additional lowering of LDL or have a genetic predisposition to high cholesterol. While PCSK9 inhibitors are undoubtedly very effective in lowering LDL levels, it is unknown if they improve long-term cardiovascular outcomes. Studies are in progress to evaluate the effect of these drugs on rate of CV events and death. Results are expected to be released in 2017. Other points of controversy with these drugs is their cost of up to $14,000 per year and target LDL goals since they are no longer supported by current guidelines. Lastly, they are administered as a subcutaneous injection into the abdomen, thigh, or upper arm every 2 weeks or once a month which could potentially be a barrier due to patient preference or ability to perform self-injections.

Side Effects

Thus far, evidence suggests alirocumab and evolocumab have a favorable side-effect profile with the most common side effects being injection site reactions at a rate of 5%. These are defined as redness, pain, and bruising at the injection site. It is important to take into account that long-term data on these drugs are not available and more side effects could be found with increased real-world experience and longer duration of treatment.

Safety and Monitoring

Both drugs are metabolized by enzymes in the gut and thus do not require dose adjustments or monitoring in patients with kidney or liver dysfunction. Patients will need baseline and repeat lipid panels to monitor for effectiveness. Patients who start this medication will need to be monitored closely for injection site reactions, allergic reactions (e.g. itchiness, rash and hives) and counseled on appropriate injection site technique and drug storage requirements.

Test Your Knowledge #3

Match the drug with its mechanism of action (use each once).

1. _____ Atorvastatin A. Inhibits the synthesis of lipoprotein and decreases production of VLDL in the liver
2. _____ Ezetimibe B. Decreases absorption of bile acids
3. _____ Colesevelam C. Inhibits HMG-CoA reductase
4. _____ Niacin D. Inhibits the absorption of cholesterol in the intestine
5. _____ Fenofibrate E. Inhibits PPAR-alpha to decrease the formation of VLDL and triglycerides

Answers on page 36.
Populations Not Addressed in the 2013 ACC/AHA Guidelines

There are multiple groups of patients who are not addressed by the current guidelines due to a lack of published trials assessing statin therapy in these groups of patients. The guideline specifically states that its recommendations are meant to support but not replace clinical judgement. In other words, omission of certain patient groups does not necessarily mean they do not qualify for statin therapy.

Age Greater than 75 Years

There is little data available to show benefit of ASCVD reduction in patients who are over 75 years of age. This group of patients requires a comprehensive review of the presence of additional risk factors (e.g. history of CHD, family history, tobacco use, presence of diabetes or hypertension), potential side effects, drug-drug interactions, drug-disease interactions, patient preferences, and priorities of care. When patients who are already on statin therapy reach the age of 75, they should continue statin use as long as there are no tolerability issues.

Heart Failure and Hemodialysis

The guidelines do not make a recommendation regarding the use of statins in patients on hemodialysis or those with New York Heart Association class II-IV heart failure. The available data suggests statins do not reduce the risk of ASCVD in these patient populations however the data was insufficient for the expert panel to make a recommendation for or against their use. Thus, similar to patients older than 75 years, statin use in patients on hemodialysis and with heart failure must be based on patient specific factors such as potential ASCVD risk reduction benefit, adverse effects, and drug-drug or drug-disease interactions.

Hypertension

Introduction to Hypertension

What is it and Who is Affected?

Hypertension (HTN) or high blood pressure (BP) is simply an elevation in pressure in the arterial wall and is measured in millimeters of mercury (mmHg). There are two values that are measured when reporting blood pressure, the systolic and diastolic BP. Systolic BP (SBP) is the top number which is achieved during cardiac contraction, when the heart is pumping blood into the arteries. Diastolic BP is the bottom number which is achieved during cardiac relaxation, when the heart is filling with blood. Normal BP is a systolic less than 120 mmHg and diastolic less than 80 mmHg where hypertension is defined as a systolic of greater than 140 mmHg or diastolic greater than 90 mmHg. Hypertension is a chronic disease with no known cure and is directly associated with CVD morbidity (disease) and mortality (death). Men and women at age 50 years that have normal blood pressures live 5 years longer than those with hypertension. Because it is a disease without symptoms, it is often referred to as “the silent killer.”

Pathogenesis and Diagnosis

What is the Cause of Hypertension?

Although the exact cause of essential hypertension is unknown there are a variety of physiologic factors that...
come into play (Figure 4, page 16). The primary determinants of systolic and diastolic blood pressure are cardiac output and total peripheral resistance (BP = CO x TPR). Cardiac output is how much blood is pumped to the body every minute and peripheral resistance is the force or pressure in the blood vessels. The renin-angiotensin-aldosterone (RAAS) and autonomic nervous system are major contributors to regulation of BP. Primarily located in the kidney, the RAAS is responsible for the production of angiotensin II which causes fluid retention, vasoconstriction (contracting of the blood vessels), vascular changes and aldosterone release. As aldosterone levels increase there is a corresponding increase in the risk of developing hypertension. The autonomic nervous system is located in the brain and periphery (e.g. veins, heart, kidney) with various components that help maintain a normal BP. Norepinephrine is a neurotransmitter that binds to alpha and beta receptors resulting in vasoconstriction, increased cardiac contractility (force of contraction) and heart rate. This component is referred to as the sympathetic nervous system (SNS). Overstimulation of RAAS, SNS or both can lead to elevations in BP. Furthermore, activation of either system also leads to activation or start of the other. In other words, activation of RAAS causes increased sympathetic stimulation and vice versa. Peripheral resistance is also affected by factors that can lead to vascular hypertrophy (thickening of the vessel wall) and decreased elasticity (stretchability). Increased fluid volume can be made worse by excess sodium (salt) intake and poor kidney function.

How is Hypertension Diagnosed?
To make the diagnosis of hypertension, a blood pressure should be measured twice at least a minute apart and the results are averaged. These values then need to be confirmed on two or more separate occasions, at least a week apart. Proper measurement technique is key to getting accurate readings. Patients should be in a seated position for at least 5 minutes with both feet flat on the floor and the arm supported at the level of the heart. No tobacco, caffeine, or medications that can raise BP should be consumed within 30-60 minutes. A proper size cuff should be fitted over a bare arm. Cuffs that are too small or large will falsely elevate or decrease BP readings, respectively. Faulty equipment will also be less accurate. Tubing should be without leaks, cuffs should remain fastened and devices should be calibrated every six months.

The SBP is the value when the first of 2 or more sounds is heard and the DBP is the value just before the disappearance of sounds. The values from the BP readings are then classified into one of four categories: normal, pre-HTN, stage 1 HTN and stage 2 HTN (Table 7).

### Table 6. Relationship between Race, Age, Gender and Prevalence of Hypertension

<table>
<thead>
<tr>
<th>Race</th>
<th>HTN prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-Hispanic blacks</td>
<td>44.9 – 46.1%</td>
</tr>
<tr>
<td>non-Hispanic whites</td>
<td>30.1 – 32.9%</td>
</tr>
<tr>
<td>Hispanics</td>
<td>29.6 – 29.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>HTN prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39 years</td>
<td>7.3%</td>
</tr>
<tr>
<td>40-59 years</td>
<td>32.4%</td>
</tr>
<tr>
<td>≥ 60 years</td>
<td>65%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age and Gender</th>
<th>HTN prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 45 years</td>
<td>Male &gt; Female</td>
</tr>
<tr>
<td>45 – 64 years</td>
<td>Male = Female</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>Female &gt; Male</td>
</tr>
</tbody>
</table>

| ≥ = greater than or equal to | < = less than | > = greater than |

### Table 7. JNC Classification of Blood Pressure

<table>
<thead>
<tr>
<th>BP classification</th>
<th>Systolic BP, mmHg</th>
<th>Diastolic BP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>And</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>Or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140-159</td>
<td>Or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥ 160</td>
<td>Or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 100</td>
</tr>
</tbody>
</table>

< = less than
≥ = greater than or equal to
Who is at Risk for Developing Hypertension?

People can develop hypertension for different reasons as there are multiple risk factors (Figure 5). These risk factors can be additive in regards to level of risk. For example, a person who is overweight, has a high sodium diet, and drinks too much alcohol will have a higher risk than someone who is just overweight. Of the non-modifiable risk factors, the relationships of age and race to prevalence of hypertension are presented in Table 6 (page 15). Inheriting hypertension from family can range from low normal BP to severe hypertension. It is likely that genetic factors along with presence or absence of other risk factors will determine the severity of hypertension.

Of the dietary factors, there is a direct relationship between obesity, insulin resistance and hypertension although the mechanism is not fully understood. For each 10% rise in weight, BP increases 6.5mmHg. Excess sodium intake can contribute to hypertension especially in the elderly, African-Americans, females and obese individuals.

In regards to lifestyle factors, socioeconomic status and lower education may be related to poor dietary choices. Smoking is an independent risk factor for the development of CVD so patients who smoke and have HTN are at a higher risk of CVD than those with HTN alone. Smoking can suddenly increase BP and HR and chronically lead to arteriole stiffness. In the Women’s Health Study, female smokers with no history of HTN or CVD were more likely to develop HTN than non-smokers. This relationship was most seen in those who smoked more than 15 cigarettes per day. Lower physical activity contributes to weight gain. However, increasing exercise even without weight loss can lower BP. Excessive alcohol intake can cause or worsen hypertension, raising BP both with short-term and long-term drinking. Risk of
HTN increases 1.5 – 2 fold in those who consume more than 2-3 alcoholic drinks/day. This risk increases as alcohol intake increases.\textsuperscript{48,49} Stress can contribute to HTN by stimulating the SNS and repeated elevations in BP during stressful situations.\textsuperscript{50}

Finally, people with pre-hypertension are more likely to develop HTN. The overall prevalence of pre-hypertension is 36%. Among men and women ages 35 to 64, the four-year incidence of developing HTN was 5.3% if their baseline BP was less than 120/80 mmHg but increased to 17.6% with a SBP of 120-129 mmHg or DBP of 80-84 mmHg and to 37.3% with a SBP of 130-139 mmHg or DBP of 85-89 mmHg. These rates were even higher for each BP category in people aged 65-94 years.\textsuperscript{51}
What are the Consequences of Hypertension?

Hypertension results in a shorter duration of life and less chance of a life free of CVD. Hypertension is a risk factor for the development of target organ damage (e.g., heart, brain, kidney). This includes stroke, CHD (angina, heart attack, and procedures to open up blood vessels), heart failure and chronic kidney disease (CKD). For every 20 mmHg increase in SBP or 10 mmHg increase in DBP, mortality (death) related to ischemic heart disease and stroke doubles starting at age 40 years. The risk between BP and CVD is unrelated to other risk factors and the higher the BP the higher the risk. Treating HTN with drug therapy can lower risk of stroke by 35-40%, heart attack by 20-25%, and heart failure by more than 50%.

Kidney function is measured by glomerular filtration rate (GFR) which is an estimate of how much blood passes through the glomeruli each minute. Glomeruli are tiny filters in the kidney that filter waste from the blood. Kidney function or GFR deteriorates with age which is made worse by high BP. When kidney disease becomes severe, it leads to the need for dialysis or transplantation. Proteinuria, the spilling of protein in the urine, is another sign of CKD. Good control of BP can slow progression of kidney disease by slowing the decline in GFR and amount of proteinuria. Other diseases associated with HTN are cognitive impairment or dementia, erectile dysfunction, obstructive sleep apnea and visual impairment.

Management/Treatment

Evaluation and Therapy Goals

In addition to the BP measurement, patients should have a complete medical assessment including physical exam, laboratory tests and history to rule out other causes of hypertension, evaluate for other CVD risk factors that may affect prognosis (outcome) and the presence of target organ damage. Based on this evaluation, initial treatment is recommended. The ultimate goal is to reduce cardiovascular related events and preserve overall health by preventing target organ damage. This can be achieved by lowering BP along with management of other risk factors for the development of CVD (Figure 6). Notice the large overlap with risk factors for hypertension and risk for the development for CVD in general.

It is well established that lowering blood pressure reduces major cardiovascular events such as stroke, coronary related events, heart failure and overall mortality. Blood pressure goals are markers for improving cardiovascular health. With that said, a blood pressure goal of less than 140/90 mmHg is recommended for the majority of the population. Specific goals for African-Americans, the elderly and patients with diabetes or CKD will be discussed later.

Lower goals may be recommended in future guidelines based on recently published studies. The SPRINT study compared the rate of CV events in patients whose BP was treated to current standards (SBP less than 140 mmHg) versus patients treated to a target SBP of less than 120 mmHg. The rate of CV events and death was less in the patients treated to the lower SBP (1.65%/year vs 2.19%/year) but patients had more side effects. An analysis of 123 studies and 613,815 patients reported that every 10 mmHg reduction in BP resulted in equal reductions in risk of major cardiovascular events.

Lifestyle Modifications

As previously discussed, lifestyle can contribute to increased BP and/or CVD risk, therefore modifications are a staple of preventing and managing hypertension. In people with a normal BP or with pre-hypertension, lifestyle modifications can prevent or delay the incidence of hypertension and therefore should be encouraged or prescribed. In people with HTN, lifestyle modifications may allow for less drug therapy or lower doses. Table 8 outlines the lifestyle modifications recommended by the Joint National Committee 7th Guideline (JNC VII) and illustrates how much BP can be lowered with each intervention. The DASH (Dietary Approaches to Stop Hypertension) eating pattern recommends eating more vegetables, fruits and whole grains and low fat dairy along with lean protein, legumes, seeds and nuts while reducing fats and added sugar. Pa-

Test Your Knowledge #4

List risk factors for hypertension.

1. ___________________ 5. ___________________
2. ___________________ 6. ___________________
3. ___________________ 7. ___________________
4. ___________________ 8. ___________________

Answers on page 36.
Overview of Hyperlipidemia and Hypertension

Table 8. BP Reduction with Lifestyle Modifications

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Average Decrease in SBP (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal BMI (18.5-24.9 kg/m²)</td>
<td>5-20 mmHg/per 10 kg weight loss</td>
</tr>
<tr>
<td>DASH eating plan</td>
<td>Diet rich in fruits and vegetables and low-fat dairy</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Goal of &lt; 2400 mg sodium/day</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Regular aerobic exercise at least 30 min/day most days of the week</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Men: Limit to ≤ 2 drinks/day</td>
<td>2-4 mmHg</td>
</tr>
<tr>
<td></td>
<td>Women: Limit to ≤ 1 drink/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 drink = 24 oz beer, 10 oz wine, 3 oz 80 proof whiskey</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; weight in kg/(height in meters)^2
DASH = Dietary Approaches to Stop Hypertension
\(< = less than\)
\(\leq = less than or equal to\)
tient education brochures can be found at http://www.nhlbi.nih.gov/files/docs/public/heart/dash_brief.pdf. The DASH diet can reduce BP in both hypertensive patients and those without hypertension.61

The 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk echoes the JNC recommendations on diet, sodium (salt) reduction and physical activity.62 It goes a step further, stating that hypertensive patients should combine the DASH dietary pattern with lower sodium intake. The general goal for consuming no more than 2400 mg of sodium/day is the same but it also states that reducing sodium intake by at least 1000 mg/day lowers BP. This is an important counselling point as patients may have a hard time adjusting to a low sodium diet so gradual reductions can be encouraged while still achieving results. Furthermore, in patients who can attain the daily sodium goal, reducing intake down to 1500mg/day may result in greater reductions in BP. In addition to the above, all smokers should be encouraged to quit in order to improve overall cardiovascular health.

**When Should Drug Therapy Be Started?**

In patients without hypertension, no drug therapy is needed and BP should be rechecked in two years.41 In patients with hypertension, drug therapy should be started if lifestyle modifications do not lower BP to less than 140/90 mmHg.41 Initiation of drug therapy in elderly hypertensive patients and those with diabetes or CKD will be addressed in the section on special populations. In patients with pre-hypertension, current recommendations are for lifestyle modifications only and BP should be rechecked every year.37,41 These recommendations may change since patients with pre-hypertension (SBP 130 mmHg or higher) were included in the SPRINT study and had improved outcomes with intensive lowering of their BP.39

**Drug Therapy Initiation and Monitoring**

There are a variety of anti-hypertensive medications available as both single and combination drugs. Both JNC VII and JNC VIII (Eighth Joint National Committee on management of high blood pressure) provide guidance on initial drug therapy or first-line treatment.41,58 JNC VIII addresses specific issues that have come to light since JNC VII was published eleven years prior. The main point of both guidelines is that initial drug choice is generally guided by race (black or nonblack) or a patient’s other medical conditions such as diabetes or CKD.

After drug therapy is started, most patients should receive follow-up at one month intervals for adjustment of medications until the BP goal is achieved. Patients with stage 2 hypertension or with complicating comorbid (e.g. diabetes, kidney disease) conditions should be followed more frequently. Most patients with hypertension will need more than one drug to get their BP to goal. There are two approaches that can be taken to adjust therapy. One is to maximize the dose of the initial drug choice before adding a second drug. The other is to use lower doses of two drugs. The latter method often will result in greater BP reductions and fewer side effects however it should be used with caution in the elderly and patients with diabetes or autonomic dysfunction (a disorder of the nerves that control BP leading to dizziness upon standing).37 This method should also be considered in patients whose BP is more than 20/10 mmHg above goal. If two drugs do not bring BP to goal, additional drugs will be added until the target BP is achieved.41 The following should be considered in patients that need more than one drug to achieve their BP goal: (1) select drugs with a different mechanism of action (2) start by selecting from drug classes in the first line drug choices since they decrease CVD (3) consider drugs from classes that may benefit comorbid conditions. Second-line choices are generally reserved for patients with resistant (hard to treat) hypertension or those who cannot take/tolerate drugs in the initial therapy list. This is because these agents have not been shown to reduce morbidity and mortality and generally have more side effects. See Figure 7 for drug classes used as first (1st) and second (2nd) line therapy.

All patients should be monitored for orthostatic (or postural) hypotension as drug therapy is being started and adjusted. Patients can become dizzy, lightheaded, or faint when they change from a flat or sitting position to standing. Orthostatic hypotension may be a barrier to good BP control. It is more common in the elderly and diabetics and may be aggravated by certain antihypertensive drugs. Patients who are taking a 1st line drug should have their kidney function and potassium checked at least 1 to 2 times per year along with monitoring for other CV risk factors. Once BP is at goal, patients should continue to have follow-up at 3 to 6 month intervals at which time adherence to medication and lifestyle modifications should be re-enforced. In patients with lower BP targets, adverse events tend to be more frequent so close monitoring is advised.
BP monitoring does not need to be limited to the office setting. Patients should also be encouraged to monitor their BP at home and report results to their healthcare providers. They should be educated on how to properly use home machines in order to ensure accurate results. The values that they measure at home can help evaluate the effectiveness of a drug regimen or uncover side effects. For example, a patient may complain of dizziness after taking their BP medications. Home BP monitoring could help identify whether their BP is dropping too low or if symptoms are more likely a side effect of the medication.

**Initial (First-Line) Therapy Drug Choices**

**Diuretics**

Diuretics (water pills) are a broad class of medications that decrease BP by promoting sodium and water excretion via small tubules in the kidney, therefore lowering the pressure on the walls of the arteries. Not all diuretics are alike as they work in different parts of the kidney and have different potencies and duration of effect. There are four subclasses of diuretics. Refer to Table 9 (page 22) for a list of drugs and doses by diuretic subclass. Other diuretics (carbonic anhydrase inhibitor and osmotic agents) also decrease volume but are not used to treat hypertension therefore will not be discussed.

Thiazide-type diuretics are a first-line choice for treating hypertension because multiple clinical trials demonstrate reduced morbidity and mortality. Hydrochlorothiazide is the most frequently used thiazide diuretic in the US, however chlorthalidone is the product used in all modern trials showing decreased CV morbidity and mortality. Thiazides are dosed once daily and can lose effectiveness in severe renal dysfunction.

Loop diuretics are more potent than thiazides but are shorter acting so may need to be dosed twice daily. They are generally reserved for patients with visible or clinical signs of volume overload such as patients with heart failure, advanced liver or kidney failure.

A common side effect associated with both thiazide and loop diuretics is hypokalemia, or low potassium. Symptoms are non-specific such as fatigue or weakness but in more severe deficiencies can lead to life-threatening abnormal heart rhythms. Therefore, potassium levels need to be monitored after initiation, dose changes, and at least 1 to 2 times/year.

Hypokalemia is treated by either increasing potassium intake through diet, supplements or the addition of a potassium-sparing diuretic such as amiloride or triamterene. These agents are weak antihypertensives so they are generally not used alone but are combined with thiazides as one product to reduce hypokalemia.

Aldosterone antagonists are also potassium-sparing and have been shown to be effective at lowering BP on their own but long term data showing decreased CV risk are not available, therefore this subclass of diuretics is not a 1st line agent. They have been shown to effectively reduce BP in patients already taking two or more antihypertensive medications and for this reason are recommended as an option for patients with resistant hypertension. Potassium-sparing diuretics should be avoided if the baseline potassium level is at the upper end of the normal range and used with caution in patients with renal dysfunction or taking other drugs that can raise potassium levels. Just as with thiazide and loop diuretics, potassium should be monitored routinely as potassium levels that are too high can also lead to life-threatening abnormal heart rhythms.
In addition to hypo or hyperkalemia, other side effects of concern are dehydration, gout, and sexual dysfunction. Dehydration can develop in the setting of vomiting or diarrhea, extreme heat, poor oral intake and can result in very low BP or kidney failure. Gout is more common with thiazides and in patients with a history of gout. Sexual dysfunction may lead to non-adherence with therapy.

**Table 9. Diuretic Drugs and Doses by Subclass**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>HTN Dosing (mg)</th>
<th>Max Daily Dose (mg)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazides</strong></td>
<td></td>
<td></td>
<td>1st line choice</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>NA</td>
<td>0.5-2</td>
<td>10</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Microzide</td>
<td>0.5-25</td>
<td>1</td>
</tr>
<tr>
<td>Indapamide</td>
<td>Lozol</td>
<td>0.5-2</td>
<td>1</td>
</tr>
<tr>
<td>Metolazone</td>
<td>Zaroxolyn</td>
<td>2.5-5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Loop</strong></td>
<td></td>
<td></td>
<td>Reserve for resistant edema</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>Bumex</td>
<td>0.5-2</td>
<td>1-2</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Lasix</td>
<td>0.5-2</td>
<td>1-2</td>
</tr>
<tr>
<td>Torsemide</td>
<td>Demadex</td>
<td>0-10</td>
<td>1</td>
</tr>
<tr>
<td><strong>Potassium sparing</strong></td>
<td></td>
<td></td>
<td>Used with thiazides to decrease hypokalemia</td>
</tr>
<tr>
<td>Amiloride</td>
<td>Midamor</td>
<td>0.5-25</td>
<td>1</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Dyrenium</td>
<td>5-10</td>
<td>1</td>
</tr>
<tr>
<td><strong>Aldosterone antagonist</strong></td>
<td></td>
<td></td>
<td>Reserve for resistant HTN (also used in HF)</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Inspra</td>
<td>0.5-2</td>
<td>1-2</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldactone</td>
<td>0.5-2</td>
<td>1-2</td>
</tr>
</tbody>
</table>

HTN = hypertension
HF = heart failure
K = potassium
> = greater than
NA = not applicable

In addition to hypo or hyperkalemia, other side effects of concern are dehydration, gout, and sexual dysfunction. Dehydration can develop in the setting of vomiting or diarrhea, extreme heat, poor oral intake and can result in very low BP or kidney failure. Gout is more common with thiazides and in patients with a history of gout. Sexual dysfunction may lead to non-adherence with therapy.

**Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers**

Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) lower BP by inhibiting the vasoconstricting effects of angiotensin II. Vasoconstriction is the narrowing of the blood vessel creating more force or pressure. Thinking of a garden hose, the narrower the tube (vasoconstriction), the more water force comes out. By widening the tube (vasodilation), there is a lower pressure and the water comes out less forcefully. Working on the RAAS, ACE inhibitors decrease the production of angiotensin II whereas ARBs bind to the angiotensin receptor in place of angiotensin II. Both classes of drugs have been proven to be effective in reducing adverse CV outcomes and therefore are an option for initial therapy. Side effects to monitor for are kidney dysfunction, hyperkalemia and orthostatic hypotension. These side effects are more frequent when ACE inhibitors and ARBs are combined with no additional benefit in CV outcomes. For this reason, in most cases, ACE inhibitors and ARBs should not be used together. Renal function and potassium should be checked after drug initiation or dose increases in addition to the routine monitoring that all hypertensive patients would have.
Overview of Hyperlipidemia and Hypertension

Table 10. ACE Inhibitors and ARBs

<table>
<thead>
<tr>
<th>ACE inhibitor</th>
<th>Brand^ Name(s)</th>
<th>Dose* (mg)</th>
<th>Doses per day</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>benazepril</td>
<td>Lotensin</td>
<td>20-40</td>
<td>1-2</td>
<td>Max 80 mg/day</td>
</tr>
<tr>
<td>captopril</td>
<td>Capoten</td>
<td>25-50</td>
<td>2-3</td>
<td>Start at 12.5mg; max 450 mg/day</td>
</tr>
<tr>
<td>enalapril</td>
<td>Vasotec</td>
<td>10-40</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td>liquid 1mg/ml</td>
<td>Epaned</td>
<td>10-40</td>
<td>1-2</td>
<td>Available as a powder for oral solution</td>
</tr>
<tr>
<td>fosinopril</td>
<td>NA</td>
<td>20-40</td>
<td>1</td>
<td>Start at 10 mg; max 80 mg/day</td>
</tr>
<tr>
<td>lisinopril</td>
<td>Prinivil Zestril</td>
<td>10-40</td>
<td>1</td>
<td>Max 80 mg/day</td>
</tr>
<tr>
<td>moexipril</td>
<td>Univasc</td>
<td>7.5-30</td>
<td>1</td>
<td>Give 1 hour before meals</td>
</tr>
<tr>
<td>perindopril</td>
<td>Aceon</td>
<td>4-8</td>
<td>1-2</td>
<td>Max 16 mg/day</td>
</tr>
<tr>
<td>quinapril</td>
<td>Accupril</td>
<td>20-80</td>
<td>1-2</td>
<td>Start at 10 mg</td>
</tr>
<tr>
<td>ramapril</td>
<td>Altace</td>
<td>2.5-20</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td>trandolapril</td>
<td>Mavik</td>
<td>2-4</td>
<td>1</td>
<td>Start 0.5-1 mg in non blacks; max 8 mg/day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ARB</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>azlisartan</td>
<td>Edarbi</td>
<td>80</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>candesartan</td>
<td>Atacand</td>
<td>8-32</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>eprosartan</td>
<td>Teveten</td>
<td>400-800</td>
<td>1 - 2</td>
<td></td>
</tr>
<tr>
<td>irbesartan</td>
<td>Avapro</td>
<td>75-300</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>losartan</td>
<td>Cozaar</td>
<td>25-100</td>
<td>1</td>
<td>Up to 150 mg/day in HF</td>
</tr>
<tr>
<td>olmesartan</td>
<td>Benicar</td>
<td>20-40</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>telmisartan</td>
<td>Micardis</td>
<td>20-80</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>valsartan</td>
<td>Diovan</td>
<td>80-320</td>
<td>1</td>
<td>Twice daily dosing in HF</td>
</tr>
</tbody>
</table>

*Start with lower doses if already taking a diuretic, has renal artery stenosis, hypovolemia or hyponatremia

^Bolded names are those drugs that are available as brand only

ACE = angiotension converting enzyme
ARB = angiotension receptor blocker
NA = not applicable
HF = heart failure

Table 10 is a list of ACE inhibitors and ARBs along with typical doses used to treat hypertension. The lower dose is the preferred starting point as patients may develop sudden hypotension with the start of drug therapy. The elderly, patients already taking a diuretic, or patients with comorbid conditions such as renal artery stenosis (narrowing of the arteries leading to the kidney), blood volume or sodium depletion, acute heart failure, or chronic kidney disease are at higher risk for developing hypotension. Starting doses in these patients should be even lower such as enalapril 2.5 to 5 mg instead of 10 mg daily.

ACE inhibitors have additional side effects of a persistent dry cough and angioedema. The cough can occur in up to 20% of patients and is bothersome which may lead to non-adherence. If the cough is due to an ACE inhibitor, it will generally resolve in 1-2 weeks after discontinuation. Angioedema is a rare but serious side effect. Patients develop swelling of the area around the eyes or lips and/ or tongue, and if severe can lead to difficulty breathing. Patients should never be treated with an ACE inhibitor again. ARBs may be an alternative if either of these side effects occur with ACE inhibitors.

Neither ACE inhibitors nor ARBs can be used during pregnancy. Women of child bearing potential should be counseled on the importance of effective birth control and to contact their physician immediately if they should become pregnant.
Calcium Channel Blockers

Calcium influx into the cellular membranes of muscles leads to contraction. Calcium Channel Blockers (CCBs) lower BP by inhibiting this influx in vascular smooth muscle thereby decreasing the contraction and pressure in the arteries. CCBs are considered for initial treatment because they are very effective at lowering BP, reduce CV events and are relatively easy to use with once daily dosing and no need for additional laboratory monitoring.

There are two subclasses of CCBs, dihydropyridine and non-dihydropyridine. They are similar in lowering BP but non-dihydropyridines also slow heart rate, decrease electrical conduction from the atria to the ventricle and decrease the force of ventricular contraction. Therefore this subclass should be avoided in patients with a baseline slow heart rate, an arrhythmia called AV (atrioventricular) block, or heart failure with low ejection fraction. Non-dihydropyridines are more likely to cause constipation, nausea or dyspepsia and fatigue where dihydropyridines are more likely to cause headaches, tachycardia (rapid heart rate) and peripheral edema (swelling of the ankles and feet). See Table 1 for a list of drugs, doses and common side effects by subclass.

Second-Line Therapy Drug Choices

Beta-Blockers

The mechanism by which beta-blockers reduce blood pressure is not fully understood and is likely a combination of reducing heart rate, cardiac output and renin (initial product of the RAAS) release. Beta-blockers are a group of drugs with different properties. Beta 1

### Table 11. Calcium Channel Blockers

<table>
<thead>
<tr>
<th></th>
<th>Brand name</th>
<th>Dose (mg)</th>
<th>Doses per day</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dihydropyridine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amlodipine</td>
<td>Norvasc</td>
<td>2.5-10</td>
<td>1</td>
<td>Peripheral edema, headache, tachycardia, dizziness, flushing</td>
</tr>
<tr>
<td>felodipine</td>
<td>Plendil</td>
<td>2.5-10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>isradipine</td>
<td>Cardene SR</td>
<td>30-60</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>nifedipine ER</td>
<td>Adalat CC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>afedibat CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nifedical XL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>procardia XL</td>
<td></td>
<td>30-120</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>nisoldipine</td>
<td>Sular</td>
<td>17-60</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Dihydropyridine</strong></td>
<td></td>
<td></td>
<td></td>
<td>Bradycardia, AV block, heart failure, constipation, dizziness</td>
</tr>
<tr>
<td>diltiazem</td>
<td>Cardizem CD</td>
<td>120-480</td>
<td>1</td>
<td>Headache, peripheral edema, asthenia (weakness), dyspepsia (indigestion), elevated liver enzymes</td>
</tr>
<tr>
<td></td>
<td>Cardizem LA</td>
<td>120-540</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cartia XT</td>
<td>120-480</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dilacor XR</td>
<td>120-480</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dilt CD</td>
<td>120-360</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diltia XT</td>
<td>180-480</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tiazac</td>
<td>120-540</td>
<td></td>
<td></td>
</tr>
<tr>
<td>verapamil</td>
<td>Calan SR</td>
<td>180-480</td>
<td>1</td>
<td>Fatigue, nausea</td>
</tr>
<tr>
<td></td>
<td>Verelan</td>
<td>120-480</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verelan PM</td>
<td>100-400</td>
<td>1 hs</td>
<td></td>
</tr>
</tbody>
</table>

* All available as generic
NA = not applicable
hs = at bedtime

AV = atrioventricular
(β1) receptors are concentrated in the heart and kidney; blocking these receptors with drug leads to decreased heart rate, cardiac output and renin release. Beta-2 (β2) receptors are concentrated in the lungs, liver, pancreas and arteriole smooth muscle; blocking these receptors with drug can lead to bronchospasm in patients with reactive airway disease, vasoconstriction, and high blood glucose in patients with diabetes. Because of these potential side effects with β2 blockade, β1 selective agents are preferred in the management of hypertension. Beta-blockers with a property called intrinsic sympathomimetic activity (ISA) are partial β agonists (activates) and are less effective in reducing CV events so generally are not used to treat hypertension. Finally, two beta-blockers have additional vaso-dilatory effects through alpha blockade. See Table 12 for a list of beta-blockers by receptor properties along with dosing.

Beta-blockers have the potential to cause fatigue, bradycardia (slow heart rate), dizziness, diarrhea, depression, erectile dysfunction, and loss of sex drive. In addition to bronchospasm and high blood glucose, non-selective agents may also cause cold extremities or worsen claudication (pain in the legs due to narrowing of the arteries) symptoms in patients with peripheral arterial disease.

If stopped abruptly, patients may experience worsening hypertension which is a sudden increase in BP to levels similar or higher than the patient’s baseline. Patients with coronary disease are at risk for developing unstable angina (chest pain), heart attack, or life-threatening abnormal heart rhythms. For this reason, if a beta-blocker needs to be stopped, doses should gradually be reduced over 1 to 2 weeks. Patients should be counseled to avoid treatment interruptions or discontinuing without advice from their physician.
Although beta-blockers are not considered an initial choice in the general hypertensive population, they reduce CV events and/or mortality in patients with coronary heart disease or heart failure with reduced ejection fraction (HFref), even in patients with a normal BP. JNC VII recommends beta-blockers as the first drug of choice in patients with stable angina, acute coronary syndrome, post-myocardial infarction and heart failure. These patients are not addressed in JNC VIII.

Alternate Antihypertensives

Alternate antihypertensives are reserved for patients whose BP remains above goal despite combining two or more drugs from the first-line agents. See Table 13 for a list of drugs by class, with dosing and other pertinent facts.

Selective alpha-1 (α1) blockers lower BP by inhibiting uptake of catecholamines such as norepinephrine in smooth muscle resulting in vasodilation. The doxazosin arm of the ALLHAT trial was stopped early due to increased CV events compared to chlorthalidone. Therefore this class of drugs should not be used alone to treat hypertension but reserved for patients with difficult to control BP and combined with one of the 1st-line agents. Concerning side effects include dizziness, fainting and orthostatic hypotension that can occur with the first dose or dose increases. Patients should be started on the lowest dose and advised to take the medication at bedtime and counseled to report unusual dizziness. Edema is common and can be reduced by combining with a diuretic. Other side effects include priapism (prolonged erection), depression, vivid dreams, nausea, diarrhea, dry mouth, fatigue or sleepiness.

Centrally (in the brain) acting α2 agonists lower BP by reducing sympathetic outflow from the brain resulting in decreased heart rate, cardiac output, renin activity and vascular resistance. Common side effects are sedation, dry mouth, urinary retention and blurred vision which are generally worse with clonidine. Fluid retention is more common with methyldopa and can be alleviated with a diuretic. Other side effects include depression, orthostatic hypotension, and dizziness. As with beta-blockers, rebound hypertension can occur with abrupt discontinuation of therapy and patients should be coun-

| Table 13. Alternate Antihypertensives (reserpine excluded) |
|---|---|---|---|---|---|
| **α1 blockers** | Brand Name | Dose (mg) | Doses per day | Max mg per day | Notes |
| doxazosin | Cardura | 1-4 | 1 | 16 | Take at bedtime |
| prazosin | Minipress | 6-15 | 2-3 | 20 | Start at 1 mg |
| terazosin | Hytrin | 1-5 | 1 | 20 | |
| **Central α2 agonists** | | | | | Rebound HTN if stopped suddenly |
| clonidine | Catapres | 0.1-0.3 | 2 | 2.4 | Patch applied weekly |
| | Catapres TTS | 0.1-0.6 | NA | | |
| methyldopa | NA | 250-500 | 2-3 | 3000 | Used in pregnancy-induced HTN |
| **Direct vasodilators** | | | | | Use with beta-blocker |
| | | | | | Often need a diuretic to prevent edema |
| hydralazine | NA | 10-50 | 4 | 300 | |
| minoxidil | NA | 5-40 | 1-4 | 100 | Reserved for very resistant HTN |
| **Renin inhibitor** | | | | | Avoid use with ACE inhibitor or ARB |
| aliskirin | Tekturna | 150-300 | 1 | 300 | |

α = alpha
HTN = hypertention
ACE = angiotensin converting enzyme
ARB = angiotensin receptor blocker
NA = not applicable
seled appropriately. Clonidine is available as a transdermal patch that is changed weekly which can help with adherence and pill burden in patients needing multiple drugs to control their BP.

Direct vasodilators lower BP by relaxing arteriole smooth muscle (i.e. dilating the vessel). Because these agents are very potent, the body tries to offset this effect by increasing heart rate, cardiac output and renin release and fluid retention resulting in decreased effectiveness over time. In patients with coronary disease, this response can lead to worsening angina. The fluid retention can cause worsening heart failure. It is recommended that patients also take a beta-blocker and diuretic to prevent these side effects. A non-dihydropyridine CCB is an option in patients who cannot take a beta-blocker. Minoxidil is the more potent agent so the elevated heart rate and fluid retention is worse than with hydralazine. Minoxidil also causes excessive hair growth.

Renin inhibitors are similar to ACE inhibitors in that they decrease the production of angiotensin II, thereby decreasing vasoconstriction and BP. One renin inhibitor is on the market and is available as branded drug only. The role of renin inhibitors is unclear since there are no data showing a reduction in CV events and the side effect profile is similar to ACE inhibitors and ARBs. Aliskiren should be avoided in pregnancy or in combination with other RAAS inhibitors; potassium and renal function should be monitored regularly.

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**Test Your Knowledge #5**
Match the drug with the drug class.

1. ____lisinopril
2. ____atenolol
3. ____hydrochlorothiazide
4. ____hydralazine
5. ____valsartan
6. ____amlodipine
7. ____clonidine

A. diuretic
B. ACE inhibitor
C. ARB
D. dihydropyridine CCB
E. beta-blocker
F. direct vasodilator
G. central alpha 2 agonist

*Answers on page 36.*

**Test Your Knowledge #6**
Match the drug class with common side effects.

1. ____ACE-inhibitors
2. ____thiazide or Loop diuretics
3. ____dihydropyridine CCB
4. ____beta-blocker
5. ____central alpha 2 agonist
6. ____alpha 1 blocker

A. bradycardia
B. sedation
C. cough
D. hypokalemia
E. peripheral edema
F. orthostatic hypotension

*Answers on page 36.*
Additional Antihypertensive Drug Information

In addition to all of the drugs listed above, many are available as combination products. For example, ACE inhibitors, ARBs, CCBs, and beta-blockers have products available with a thiazide diuretic. Some ACE inhibitors and ARBs are also available in combination with amlodipine. The dose combinations are the most common doses used to manage hypertension. These products are useful in decreasing pill burden and may improve adherence.

Most of the drug classes described also have indications for treatment of other diseases. Selection of a particular drug may be driven by other diseases the patient has, or a patient may be taking one of these drugs without a diagnosis of hypertension. Refer to Table 14 for drug classes that have alternate uses.

Hypertensive Crises

When Should Patients Seek Urgent Care?

Hypertensive crises is defined by a BP greater than 180/120 mmHg. If the patient is having signs of target organ (heart, kidney, brain) injury, this is considered an “emergency” and BP needs to be lowered within hours. Target organ injury is based on symptoms in the vital organs and can be the presence of any of the following: encephalopathy (decreased mental status), intracranial hemorrhage (bleeding into the brain), acute heart failure, acute myocardial infarction, or pulmonary edema (fluid in the lungs). If no organ damage is present, then it can be considered an “urgency” in which case BP can be lowered over several hours to days with oral therapy. Adding drugs, increasing doses, or restarting the base regimen in non-adherent (non-compliant) patients are all options. Rapid reductions in BP should be avoided as it could cause sudden myocardial infarction, sudden kidney injury or stroke.

Special Populations

Treating Hypertension in the Elderly

The prevalence of HTN increases with age as shown in Table 1 (page 3). Isolated systolic hypertension (ISH) is defined as a SBP greater than 140 mmHg with a normal DBP and is the predominant form of hypertension in people over the age of 60 years. As SBP rises, there is an equal rise in the risk of stroke. There are numerous

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Additional Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors or ARB</td>
<td>Asymptomatic left ventricular dysfunction Heart failure Prevention of CV events in high risk patients Acute myocardial infarction Nephropathy</td>
</tr>
<tr>
<td>Calcium channel blockers: Dihydropyridine Non-dihydropyridine</td>
<td>Chronic stable angina Vasospastic angina Atrial fibrillation or flutter Paroxysmal supraventricular tachycardia</td>
</tr>
<tr>
<td>Diuretics Loop and thiazide Aldosterone antagonist</td>
<td>Edema Heart failure</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Angina Prevent CV events post-MI Heart Failure (bisoprolol, carvedilol, metoprolol succinate only)</td>
</tr>
<tr>
<td>α1 blockers</td>
<td>Benign prostatic hypertrophy</td>
</tr>
<tr>
<td>Direct vasodilators</td>
<td>Heart failure (hydralazine only and in combination with nitrates)</td>
</tr>
<tr>
<td>ACE = angiotensin converting enzyme ARB = angiotensin receptor blocker α1 = alpha 1</td>
<td>CV = cardiovascular MI = myocardial infarction</td>
</tr>
</tbody>
</table>
clinical trials demonstrating decreasing BP leads to decreased CV events and mortality in the elderly including one trial in those over 80 years old. Treatment targets vary between guidelines. There is a consensus that all elderly patients should achieve a BP of less than 150/90 mmHg however most guidelines other than JNC VIII recommend a lower target of less than 140/90 mmHg for age less than 80 years. The SPRINT trial may affect future guideline recommendations as the average age of participants was 68 years with 30% being age 75 or greater. The treatment benefit with achieving the lower BP of less than 120/80 mmHg in the elderly was consistent with the overall study results.

Drug therapy choices for initial therapy are about the same as the general population and JNC VIII does not give a preference for which drug class to start with. However, elderly patients are at risk for orthostatic hypotension so doses should always start lower and BP lowered gradually with frequent monitoring. Comorbidities and frailty should be taken into consideration for drug selection and target BP goals.

**Treating Hypertension in Patients with Diabetes**

Diabetic patients generally have a higher incidence of HTN than the general population and people with hypertension are 2.5 times more likely to develop diabetes. These diseases are also linked because both are associated with increased risk of morbidity and mortality from CVD. Diabetes alone is a risk factor for the development of CVD and diabetics have a 70-80% chance of premature death from CVD. Good control of BP is imperative to reduce risk. The treatment goal for diabetics varies by guidelines. At a minimum, all patients regardless of age should achieve a BP of less than 140/90 mmHg. Other guidelines recommend a lower goal of less than 130/80 mmHg.

Initial therapy selection is the same as the general population and comorbid conditions should be considered as in Table 14. Multiple agents are often needed to control BP. ACE inhibitors and ARBs have been shown to decrease cardiovascular risk and progression of chronic kidney disease. Although JNC VIII does not make a specific recommendation for this class, diabetes guidelines state that either an ACE inhibitor or ARB is preferred.

**Treating Hypertension in Patients with Chronic Kidney Disease**

As with diabetes, CVD is the most common cause of death in patients with chronic kidney disease (CKD) and CKD is a risk factor for developing CVD. CKD is defined as a decline in glomerular filtration rate (GFR) to less than 60 mL/min (normal is usually 90 mL/min or higher) or proteinuria at greater than 300mg/day. Good control of BP can slow the decline in GFR or the development of proteinuria. Also similar to diabetes, there is a consensus among guidelines, including JNC VIII, that all patients with CKD should be treated to a target of less than 140/90 mmHg. In patients with proteinuria a lower target of less than 130/80 mmHg is recommended by some medical societies.

All CKD patients regardless of race or presence of diabetes should be treated with an ACE inhibitor or ARB. This is because these agents are more effective at delaying decline in renal function. Potassium is excreted through the kidney and patients with advanced CKD are at risk for hyperkalemia (elevated potassium in the blood). Because ACE inhibitors and ARBs also cause potassium retention, potassium levels should be monitored closely.

**Treating Hypertension in African-Americans**

African-Americans have a higher prevalence of hypertension, have more target organ damage, and are more likely to need combination drug therapy to achieve their BP goal than the general population. ACE inhibitors, ARBs and beta-blockers are less effective when used as monotherapy (single therapy) but can achieve similar BP reductions to Caucasians when a thiazide diuretic is added. JNC VIII recommends that initial therapy should include a thiazide diuretic or CCB whether or not the patient has diabetes.

**Conclusion**

Hyperlipidemia and hypertension are both major risk factors for developing CVD. Because each disease is asymptomatic, it is important for patients to understand that treatment goals revolve around prevention of heart attack, stroke and kidney disease. Lifestyle modifications should be emphasized and reinforced as they can help patients achieve their treatment goals, however, many patients will still need drug therapy.
There are many medications to choose from to treat hyperlipidemia and hypertension. Each disease has national guidelines with recommendations for initial therapy as these drugs have been proven to improve morbidity and mortality related to CVD. Many pharmacies have blood pressure monitors and some provide point of care (i.e. finger stick) testing of cholesterol profiles which can prompt questions from patients. Pharmacy technicians should be familiar with normal and abnormal values along with common medications and their side effects that are used to treat hypertension and hyperlipidemia. Pharmacy technicians can assist pharmacists and providers by promoting adherence (compliance with medication regimen), identifying side effects and facilitating patient education through a pharmacist.

**Test Your Knowledge #7**

Which patient populations may require a different BP goal? Circle all that apply.

- African-Americans
- Patients older than 60 years
- Patients with diabetes
- Patients with high cholesterol
- Patients with chronic kidney disease

*Answers on page 36.*

**Patient Case #2**

Mrs. Brown is a 58 year old female who is at the office for a routine check up. Her BP is 136/86 mmHg (repeated BP is 138/84 mmHg). She smokes ½ pack per day which is improved from 1 pack per day a year ago.

Are you concerned about her blood pressure readings?

What can she do to decrease her risk?

*Answers on page 36.*

**Patient Case #3**

Mr. Green is a 45 year old male with a strong family history of heart disease and hypertension. His BP is 150/94 mmHg (repeat 152/90 mmHg) after 3 months of lifestyle changes.

Which drug or drug class would be appropriate for a doctor to prescribe to treat his hypertension?

*Answers on page 36.*
References


Overview of Hyperlipidemia and Hypertension


24. ZOCOR (simvastatin) [package insert]. Whitehouse station, NJ; Merck; revised March, 2015.


26. ZETIA (ezetimibe) [package insert]. Whitehouse station, NJ; Merck; revised August, 2013.


34. REPATHA (evolocumab) [package insert]. Thousand Oaks, CA; AMGEN; Revised August, 2015.

35. PRALUENT (alirocumab) [package insert]. Bridgewater, NJ; sanofi-aventis; Revised October, 2015.


ANSWER KEY: TEST YOUR KNOWLEDGE EXERCISES

Exercise #1:
Modifiable: hypertension, cigarette smoking, diabetes, obesity, physical inactivity, diet
Non-modifiable: age, gender, family history

Exercise #2:
1. LDL-C = 200 – 60 – 125 / 5 = 200 – 60 – 25 = 115 mg/dL
2. Above optimal

Exercise #3:
1. C
2. D
3. B
4. A
5. E

Exercise #4:
Age, race, family history, pre-hypertension, obesity, high sodium diet, excessive alcohol, smoking

Exercise #5:
1. B
2. E
3. A
4. F
5. C
6. D
7. G

Exercise #6:
1. C
2. D
3. E
4. A
5. B
6. F

Exercise #7:
older than 60 years, diabetes, chronic kidney disease

Patient Case #1:
1. The patient is not correct in making this claim. Statin therapy has always been studied and is meant to be used in conjunction with lifestyle modifications such as a heart-healthy diet that is low in saturated fats, increased physical activity, smoking cessation and weight loss.
2. Yes, the pharmacist should be alerted. First, the patient takes atorvastatin which is a lipophilic statin. Increased lipid solubility is associated with an increased risk of muscle side effects. Second, although the timing of the muscle pain is correlated to physical activity, the pain has not resolved in 5 days which may indicate the patient may be having muscle toxicity that should be evaluated further by a pharmacist.

Patient Case #2:
Are you concerned about her blood pressure readings?
Yes, because she would be classified as pre-hypertension (Table 7) which puts her at a 37% risk of developing hypertension.

What can she do to decrease her risk?
She can make changes to her lifestyle such as:
- Quitting smoking
- Decreasing sodium (salt) in her diet
- Follow a DASH diet
- Increase her physical activity

Patient Case #3:
Which drug or drug class would be appropriate to treat his hypertension?
He has stage 1 hypertension (Table 7) so he should start drug therapy.
A thiazide diuretic, ACE inhibitor, ARB or calcium channel blocker are all appropriate 1st-line choices (Figure 7)
SELF ASSESSMENT QUESTIONS

1. Which of the following is NOT associated with an increased risk of developing coronary heart disease?
   A. Cigarette Smoking
   B. Hypertension
   C. Age
   D. Migraine headaches

2. What organ is primarily responsible for the regulation of cholesterol in the body?
   A. Pancreas
   B. Liver
   C. Heart
   D. Brain

3. Which of the following is TRUE with regards to cholesterol?
   A. The level of cholesterol reported on a lipid panel is not affected by fasting state
   B. LDL is sometimes referred to as the “good” cholesterol
   C. Lipoprotein lipase is the rate-limiting enzyme in intracellular synthesis of cholesterol
   D. LDL particles contain 60-70% of all blood cholesterol

4. Which drug class is recommended to use as first-line according to the 2013 ACC/AHA Cholesterol Guidelines?
   A. Niacin
   B. PCSK9 inhibitors
   C. Statins
   D. Cholesterol absorption inhibitors

5. Which drug and dose is considered a high-intensity statin?
   A. Ezetimibe 10 mg
   B. Pravastatin 40 mg
   C. Atorvastatin 80 mg
   D. Simvastatin 40 mg

6. What is the most common side-effect of niacin?
   A. Injection-site reactions
   B. Flushing
   C. Myopathy
   D. Constipation

7. What drug class is primarily used for the treatment of hypertriglyceridemia?
   A. Bile-acid sequestrants
   B. Fibrates
   C. Statins
   D. Cholesterol-absorption inhibitors

8. What drug is approved for use as an add-on to statin or fibrate therapy?
   A. Colestipol
   B. Colesevelam
   C. Ezetimibe
   D. Fenofibrate

9. Which drug must be administered via a subcutaneous injection?
   A. Evolocumab
   B. Simvastatin
   C. Niacin
   D. Ezetimibe

10. What patient population is least likely to benefit from using statin therapy based on the current evidence and guideline recommendations?
    A. Prior myocardial infarction
    B. Diabetic
    C. Heart failure
    D. Prior stroke

11. Hypertension is defined as greater than?
    A. 120 mmHg systolic or 80 mmHg diastolic
    B. 130 mmHg systolic or 85 mmHg diastolic
    C. 140 mmHg systolic or 90 mmHg diastolic
    D. 150 mmHg systolic or 95 mmHg diastolic

12. Which of the following is NOT a risk for the development of high blood pressure?
    A. Age and family history
    B. Elevated cholesterol
    C. Obesity
    D. Excessive alcohol intake
13. Which is NOT a consequence of hypertension?
   A. Development of stroke
   B. Development of chronic kidney disease (CKD)
   C. Development of diabetes
   D. Development of coronary heart disease (CHD)

14. Which diuretic is appropriate for initial treatment of hypertension?
   A. Chlorthalidone
   B. Furosemide
   C. Spironolactone
   D. Amiloride

15. Which statement about ACE inhibitors and ARBs is TRUE?
   A. Using them together is recommended as initial therapy
   B. They can be used in pregnancy
   C. They need regular monitoring of potassium levels
   D. Cough is a common side effect of both

16. Which statement is TRUE about calcium channel blockers (CCBs)?
   A. Dihydropyridines are better at lowering blood pressure
   B. Headache and edema are common side effects
   C. All of the CCBs slow heart rate
   D. They should be avoided in patients with chronic stable angina

17. Which statement is TRUE about beta-blockers?
   A. Tachycardia is a common side effect
   B. All beta-blockers inhibit β1 and β2 receptors
   C. Sudden discontinuation can lead to sudden increases in BP
   D. They should be avoided in patients with coronary heart disease (CHD) or heart failure

18. Which drug is NOT an alternate antihypertensive?
   A. Clonidine
   B. Verapamil
   C. Hydralazine
   D. Doxazosin

19. Which statement about treating hypertension in the elderly is TRUE?
   A. BP should be lower than 150/90 mmHg
   B. Starting doses of medications are the same as the general population
   C. As systolic BP rises, the risk of stroke is decreased
   D. Decreasing the BP has no effect on CV events or mortality

20. Which statement about African-Americans and hypertension is TRUE?
   A. Prevalence and organ damage are similar to other races
   B. ARBs should be the first drug selected
   C. Thiazide diuretics or CCBs should be the first drug selected
   D. Single drug therapy is likely to achieve their BP goal