The primary aim of Operation Heart is to assist patients with understanding and managing their risks for cardiovascular disease (CVD). Because global risk is determined by the presence of multiple risk factors, patients should also be aware of their non-modifiable risks, as this may provide additional incentive to manage the risk factors that remain under their control. Presence of one or more of the risk factors below is rarely an indication for pharmacotherapy; however, it may provide critical information to health care providers assessing the additive risk imparted by multiple risk factors.

**Age**

Age is an independent predictor of risk for CVD in both men and women. Although this increase in risk is not well understood, it is likely multifactorial. As described previously in this guide, atherosclerosis is a chronic inflammatory condition that progresses with age. In addition, evidence from epidemiologic studies indicates a predictable age-related increase in the incidence of hypertension, which further increases the risk imparted by age alone.

Guidelines for the prevention of CVD generally recognize that age becomes an independent risk factor in men after age 45 and in women after age 55. While these thresholds predict an increased risk of global CVD, they differ for specific cardiovascular disorders. For example, with hypertension, age becomes a risk factor at 55 and 65 years of age for men and women, respectively.

The average risk for CVD appears to plateau at 80 years of age [1]. In older patients, the benefit of medication therapy must be carefully weighed against the risk of adverse effects.

**Gender**

As demonstrated above, the increased risk attributed to age differs based on gender. With the exception of patients greater than 80 years of age, the risk of heart disease at each decade of life is greater in men than women [1]. Furthermore, comparable levels of risk in women appear to lag approximately 10–15 years behind those in men [2]. This difference in cardiovascular risk is not well‐elucidated but is thought to be multifactorial. The earlier onset of cardiovascular risk factors such as hypertension and hyperlipidemia may be partly to blame. However, an analysis from the Framingham Heart Study indicates that these differences cannot be attributed to traditional risk factors alone [2].

The increased risk of CVD among women occurs shortly after menopause, which led many to believe that estrogen might play a cardioprotective role in women. While estrogen has beneficial effects on lipid and carbohydrate metabolism, two large clinical trials in postmenopausal women demonstrated that hormone replacement with estrogen‐only or combined estrogen‐progestin therapy actually increased the risk of CVD [3, 4]. As a result, hormone replacement therapy is not recommended as a strategy for reducing CVD risk in postmenopausal women and should generally be avoided in those with established CVD.

**Family History**

A positive family history of CVD among primary relatives (i.e., parents and siblings) is also an independent risk factor for heart disease. A two-fold increase in CVD risk was found among patients enrolled in the Framingham Heart Study [5, 6], while other studies estimate risks as high as 12-times that of the general population [2]. Modifiable risk factors such as physical inactivity and poor diet are thought to play a role, but a positive family history of CVD remains an independent risk factor even when other influences are excluded [7, 8]. Although genetic markers associated with CVD risk have
been discovered, these have not been shown to significantly impact risk prediction beyond what is already been imparted by family history.

Similar to the risk factors described above, the increased risks imparted by family history also differ based on gender. A positive family history (and thus, an independent risk factor for CVD) is defined as coronary artery disease or sudden death in a first degree male relative (e.g., father or brother) under 55 years of age, or a first degree female relative (e.g., mother or sister) under 65 years of age.

Ethnicity
While ethnicity is not considered a traditional CVD risk factor based on data from the Framingham Heart Study, evidence from epidemiologic analyses has shown differences in the incidence and prevalence of some cardiovascular disorders based on ethnicity. The prevalence of overall heart disease is highest among Caucasians at 11.1%, but African Americans have the highest mortality rate at 387.0 and 267.9 per 100,000 males and females, respectively [9, 10]. Rates of hypertension are also much higher in African Americans and Hispanics while Asian Americans have the lowest rates of heart disease, hypertension, and stroke [9]. The prevalence of preventable risk factors is highest among African Americans and American Indians, where nearly 50% of patients have at least two identifiable risk factors [11].

Evaluating the influence of ethnicity on cardiovascular morbidity and mortality is complex, due in part to the difficulty of distinguishing genetic or environmental differences from health disparities, which are differences in the access to or quality of health care across different ethnic groups.
References

Important note: Some of the information included here has been adapted from the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [1]. As of this writing, updates to the guidelines were being made but were not yet available for review.

Lipids are a class of water-insoluble organic molecules that play a critical role as precursors for cell membranes and other important endogenous compounds. Also known as “fats”, lipids include cholesterol and cholesterol esters, phospholipids, and triglycerides. The term dyslipidemia refers to abnormal concentrations of one or more of these lipids in the serum whereas hyperlipidemia refers to elevated lipid concentrations. Abnormal concentrations of specific lipids in the serum are strongly correlated with development of cardiovascular disease (CVD), providing a target for risk reduction therapy.

Cholesterol is transported in the blood via protein carriers; together, these complexes are known as lipoproteins. Lipoproteins are classified according to density and include low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very low density lipoprotein (VLDL). A measure of total cholesterol (TC) includes all three of these lipoproteins, so a fasting lipid panel is often used to determine the value of each specific carrier. Low density lipoprotein (often called “bad cholesterol”) is considered the most atherogenic of the three and is identified by national guidelines as being the primary target of therapy [1], although some controversy surrounds its use as a surrogate marker for CVD. A high concentration of HDL ("good cholesterol") is associated with reductions in CVD risk but medication therapies specifically targeting HDL have yet to produce improvements in clinical outcomes.

A small minority of patients with specific types of dyslipidemia may experience symptoms but most remain asymptomatic for many years. During this time, abnormal lipid concentrations contribute to the development of atherosclerosis and most patients eventually present with heart disease. As with hypertension, the asymptomatic nature of dyslipidemia often delays appropriate management, placing patients at risk for adverse outcomes. Through screening and education events, student pharmacists can play an important role in helping patients identify their risks for CVD. For those already receiving therapy, these activities can help patients determine progress toward goals established by their providers.

Important Note: As a reminder, the terms coronary artery disease (CAD), coronary heart disease, and ischemic heart disease are often used interchangeably in the literature. For example, the NCEP guidelines refer to cardiovascular risks in terms of 10-year risk of coronary heart disease, or CHD. For the sake of consistency, only the term coronary artery disease or CAD will be used to describe ischemic heart disease in this module. Please note that the term cardiovascular disease or CVD is a broader term that may include CAD, stroke, and a variety of other disorders.

Dyslipidemia as a Cardiovascular Risk Factor
Dyslipidemia emerged as an important clinical entity due to its strong association with the development of CAD and CAD-related mortality [2, 3]. For patients with established disease, elevations in LDL correlate with higher rates of recurrent events [4]. While some controversy remains as to whether LDL should serve as the primary target of risk reduction therapy, many clinical trials aimed at reducing LDL have demonstrated clear reductions in cardiovascular morbidity and mortality [5, 6]. Epidemiologic studies indicate that CAD incidence appears to correlate with serum LDL concentrations.
(i.e., the higher the serum LDL concentration, the higher the rate of adverse outcomes) [3], although results have been inconsistent in prospectively conducted clinical trials and especially among patient populations with lower mean LDL concentrations. Unfortunately, an alternative surrogate marker for CVD has yet to emerge, so LDL has remained the primary target of antidyslipidemic therapy.

Additional investigations have linked other lipids to increased risks for developing CAD. A meta-analysis of 17 prospective population-based studies found that elevated triglycerides are an independent risk factor for CAD [7]. Additionally, low serum concentrations of HDL are also an independent risk factor for CAD [8]. Epidemiologic evidence indicates that a 1% decrease in HDL corresponds to a 2-3% increase in CAD risk [9]. As a result of these and other studies, several components of the lipid panel may serve as secondary targets of therapeutic lifestyle changes and/or medication therapy in select patients.

**Epidemiology**
Although averages have improved in recent years, over 30 million American adults (about 13.8% of the US population) are estimated to have total serum cholesterol levels above those recommended by national guidelines [10]. Awareness of the condition has also improved, although between half and two-thirds of patients are unaware they have high cholesterol [11, 12]. Less than half of patients who qualify for lipid-modifying therapy are receiving it, including those considered at highest-risk of CAD [1]. Of those receiving therapy, only one-third are at goal.

**Etiology & Pathophysiology**
Lipid disorders are broadly classified based on the specific abnormality (e.g., hypertriglyceridemia). Both primary (genetic) and secondary forms of lipid disorders exist (Table 1) and patients with abnormal lipid panels may have underlying components of both.

Primary dyslipidemias are commonly the result of genetic defects in lipid carriers or other components of the lipid metabolism and transport system. Secondary dyslipidemias often result from concomitant disease states or as part of an unhealthy lifestyle (e.g., poor diet, lack of exercise). Irrespective of etiology, the pathogenesis of dyslipidemia is an accumulation of certain lipid types and development of atherosclerosis, leading to CAD. To understand the pathophysiology of dyslipidemia, it is important to understand the mechanisms of normal lipid physiology.

Lipids are essential to life and are categorized primarily as cholesterols, phospholipids, or triglycerides. As hydrophobic molecules, lipids require protein carriers to be transported through the serum. Three main pathways transport lipids throughout the body: the endogenous, exogenous, and reverse cholesterol transport pathways. In the exogenous pathway, lipids are absorbed from the diet and delivered by lipoprotein carriers to peripheral tissues for energy production or to the liver for use in biosynthetic reactions.

![Table 1. Secondary Causes of Lipoprotein Abnormalities](image-url)

Adapted from Reference 13
The process by which the liver packages lipids for delivery to peripheral tissues is known as the endogenous pathway. The reverse cholesterol transport pathway is the process by which lipids are scavenged in peripheral tissues and transferred back to the liver.

Low density lipoprotein is the primary carrier of cholesterol in the blood. Low density lipoprotein binds to receptors on peripheral cells, where it is converted into cholesterol esters for use in cellular biosynthesis. When adequate concentrations of intracellular cholesterol are reached, peripheral cells down-regulate their LDL receptors, thus reducing the amount of LDL absorbed and increasing the concentration of LDL remaining in the serum. Excess LDL is engulfed by macrophages, which become foam cells upon endocytosis of lipids and the oxidative metabolism that follows. Foam cells are a major component of the atherosclerotic process (see Disease State Overview).

Clinical Evaluation

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) published clinical guidelines for the detection, evaluation, and management of high blood cholesterol [1]. An update was published in 2004 to include results from several major trials involving the use of statin therapy [14].

In order to determine the intensity of risk-reduction therapy, the first step in clinical evaluation of dyslipidemia is an assessment of a patient's overall risk. As mentioned above, LDL is the primary target of antidy sperm lipidemic therapy and should be measured as part of the overall risk assessment. For patients over the age of 20, a fasting lipid panel (FLP) is recommended every 5 years (fasting is defined as having not eaten within 9-12 hours of measurement). An FLP should include TC, LDL, HDL, and triglycerides. If the patient is non-fasting, only TC and HDL values are accurate, as triglycerides are significantly affected by food. According to the ATP III Guidelines, an LDL of < 100 mg/dL is considered optimal. A full summary of lipid classifications can be found in Table 2.

While LDL is a risk factor for the development of CAD, the intensity of LDL-modifying therapy is based on the presence or absence of other components, including established CVD, other forms of atherosclerotic disease, and major risk factors. For the purpose of risk stratification, the presence of diabetes is considered equivalent to CAD (known as a “risk equivalent”). The other major risk factors identified by ATP III are shown in Figure 1.

Table 2. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dl)

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (TC)</td>
<td>&lt; 200</td>
<td>Desirable</td>
</tr>
<tr>
<td></td>
<td>200 – 239</td>
<td>Borderline high</td>
</tr>
<tr>
<td></td>
<td>&gt; 240</td>
<td>High</td>
</tr>
<tr>
<td>Low-density lipoprotein (LDL)</td>
<td>&lt; 100</td>
<td>Optimal</td>
</tr>
<tr>
<td></td>
<td>100 – 129</td>
<td>Above optimal</td>
</tr>
<tr>
<td></td>
<td>130 – 159</td>
<td>Borderline high</td>
</tr>
<tr>
<td></td>
<td>160 – 189</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>&gt; 190</td>
<td>Very high</td>
</tr>
<tr>
<td>High-density lipoprotein (HDL)</td>
<td>&lt; 40</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>≥ 60</td>
<td>High</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 150</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>150 – 199</td>
<td>Borderline high</td>
</tr>
<tr>
<td></td>
<td>200 – 499</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>≥ 500</td>
<td>Very high</td>
</tr>
</tbody>
</table>

Adapted from the NCEP ATP III Guidelines [1]

Figure 1. Major risk factors for Heart Disease (Exclusive of LDL Concentration)

- Age (men ≥ 45, women ≥ 55 years of age)
- Family history of premature CHD (males < 55, females < 65 years of age)
- Hypertension (BP ≥ 140/90 mmHg or on antihypertensive therapy)
- Low HDL cholesterol (< 40 mg/dL); HDL ≥ 60 mg/dL counts as a “negative” risk factor
- Cigarette smoking
Goals
Based on the presence or absence of CAD and other major risk factors, ATP III further stratifies the LDL goal (Table 3). While treatment is based on attaining a specific LDL goal, the primary reason for initiating therapy is to prevent long-term adverse outcomes, including myocardial infarction, stroke, and other forms of atherosclerotic disease. Risk equivalents for CAD include peripheral arterial disease, symptomatic carotid artery disease, abdominal aortic aneurysm, diabetes, and a composite of risk factors conferring a 10-year risk for CAD > 20%. While the goal LDL in these patients is < 100 mg/dl, a 2004 update to the guidelines includes an optional goal of < 70 mg/dl in these high-risk patients [14].

 Patients without established CAD or risk equivalents must be evaluated by the number of risk factors present and overall 10-year risk. First, the number of risk factors must be counted (Figure 1). Because some risk factors confer a greater risk of heart disease than others, a patient’s 10-year risk for CAD must be calculated. A common tool for calculating 10-year risk is the Framingham Risk Score, although others may be used (see section on General Considerations). For patients with two or more risk factors and a 10-year CAD risk of 20-20%, an LDL goal of < 130 mg/dl is appropriate; if patients have two or more risk factors and a 10-year CAD risk > 20%, their risk becomes a CAD risk equivalent and the LDL goal is < 100 mg/dl (or < 70 mg/dl).

<table>
<thead>
<tr>
<th>Table 3. Risk Categories and Corresponding LDL Goals [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Category</td>
</tr>
<tr>
<td>CAD or risk equivalents (atherosclerotic disease, diabetes, or risk factors with composite CAD risk &gt; 20%)</td>
</tr>
<tr>
<td>2 or more risk factors (and CAD risk 10-20%)</td>
</tr>
<tr>
<td>0-1 risk factor</td>
</tr>
<tr>
<td>CAD coronary artery disease, LDL low-density lipoprotein, TLC therapeutic lifestyle changes</td>
</tr>
<tr>
<td>*An LDL goal of &lt; 70 may be considered</td>
</tr>
</tbody>
</table>

Management
Therapeutic lifestyle changes (TLC) should be recommended for patients who are not at LDL goal and prior to the initiation of pharmacotherapy. Components of TLC known to improve LDL include reduced intake of dietary fats and cholesterol, increased intake of LDL-lowering foods such as plant stanols/sterols and soluble fiber, weight reduction, and increased physical activity (see Diet and Lifestyle). Except in those with established CVD (e.g., history of CAD or stroke), an adequate trial (i.e., 6 weeks) of TLC should be provided to all patients. Patients with LDL levels far exceeding their goal may be considered for drug therapy at onset, although a trial of TLC is also reasonable prior to the initiation of drug therapy.

For patients unable to reach LDL goals with TLC, the emphasis of lipid management shifts to medication therapy, requiring referral to a provider for further evaluation and management. The most extensively studied antihyperlipidemic agents are the HMG-CoA reductase inhibitors, commonly known as statins. Statins have been shown in various trials to reduce LDL as well as improve

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cardiovascular outcomes. Other agents may also be considered based on their effects on LDL or other components of the lipid panel. A list of antihyperlipidemic agents can be found in Table 4.

<table>
<thead>
<tr>
<th>Table 4. Commonly Used Antihyperlipidemic Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitors (Statins)</td>
</tr>
<tr>
<td>Fibrates</td>
</tr>
<tr>
<td>Bile Acid Resins</td>
</tr>
<tr>
<td>Niacin</td>
</tr>
<tr>
<td>Fish oil</td>
</tr>
<tr>
<td>Absorption Inhibitors</td>
</tr>
</tbody>
</table>
References

Important note: Some of the information included here has been adapted from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [1]. As of this writing, updates to the guidelines were being made but were not yet available for review.

Blood pressure (BP) is a measurement of the force exerted by circulating blood on the arterial wall and is described in terms of the systolic blood pressure (SBP) and diastolic blood pressure (DBP). The SBP reflects the circulatory pressure exerted during cardiac contraction (maximum pressure) while DBP reflects pressure during relaxation (minimum pressure). Both values are measured in terms of millimeters of mercury (mmHg), and blood pressure is commonly reported as the SBP value over the DBP value (i.e., 120 / 80 mmHg).

While a variety of stimuli can temporarily raise or lower blood pressure, hypertension is a pathologic state characterized by sustained blood pressures of 140/90 mmHg or higher. Left untreated, elevated pressures can damage small blood vessels in the eyes, kidneys, heart, brain, and other vital organs. Over time, the body's physiologic response to elevated pressures may lead to vascular remodeling, which can leave blood vessels fibrotic and less able to respond to changes in hemodynamic status. Unfortunately, many patients with hypertension are asymptomatic, often delaying diagnosis and appropriate management.

Hypertension as a Risk Factor for Cardiovascular Disease
Data from the Framingham Heart Study demonstrated unequivocally the role of hypertension as an independent risk factor for cardiovascular disease (CVD) [2]. Hypertension is directly implicated in the pathophysiology of diastolic heart failure and is also a risk factor for myocardial infarction and stroke. The definition of hypertension as blood pressures exceeding 140/90 mmHg threshold is somewhat misleading, as epidemiologic studies have revealed a continuous and positive risk of CVD mortality at values as low as 115/75 [3]. In fact, for every 20 mmHg increase in SBP or 10 mmHg increase in DBP, the risk of CVD-related mortality doubles [3]. Moreover, the presence of other CVD risk factors further multiplies the risk imparted by hypertension [4].

The goal of measuring blood pressure at community outreach activities is to raise awareness of hypertension and to identify those patients for whom a more comprehensive cardiovascular risk evaluation may be necessary. Because so many patients are asymptomatic, student pharmacists can have a significant impact on the prevention of CVD by helping patients become aware of their risks. For patients already being treated for hypertension, student pharmacists can also assess the adequacy of therapy, reinforce the importance of medication adherence, and if necessary, refer them to their provider for further evaluation.

Epidemiology
Hypertension is the most common cardiovascular disorder in America. Current estimates indicate that nearly 1 in 3 adults (about 77.9 million) have high blood pressure [5]. The prevalence of hypertension also increases with age—half of patients over the age of 60 will develop hypertension in their lifetime and by age 80-85, these rates approach 90% [6, 7]. Although most patients die from an acute event related to hypertension, over 60,000 die from hypertension annually [5]. As a result, the benefits of preventing hypertension are significant, as epidemiologic analyses indicate non-hypertensive patients live approximately 7 years longer than those with hypertension [9].
Hypertension awareness has improved over the last several decades, but just 4 out of every 5 patients are aware they have the condition. Nearly 75% of patients with hypertension are treated with medication therapy, but only half are adequately controlled according to guidelines [5, 10]. Management is especially dismal among elderly patients, where control rates average around 30% [11].

In addition to the morbidity and mortality associated with the disorder, hypertension costs the US health care system over $50 billion annually, an amount that is estimated to become $343 billion by the year 2030 [5].

**Etiology and Pathophysiology**

Physiologic regulation of arterial blood pressure is subject to multiple factors, making the process of identifying a definitive cause for hypertension difficult in many patients. For patients in whom an underlying cause cannot be identified, hypertension is classified as being primary or essential. A small minority of patients will present with an identifiable cause for elevated blood pressures and are therefore classified as having secondary hypertension. In most cases, treating the underlying cause of secondary hypertension is the most successful management strategy. A list of common etiologies for secondary hypertension is provided in Table 1.

Although physiologic regulation of blood pressure is complex and multifactorial, its mechanisms can be broadly classified as being neurohormonal, renal, or vascular in nature. Hypertension is commonly the result of maladaptive changes in one or more of these compensatory systems.

The neurohormonal mechanism of hypertension involves hyperactivity in the sympathetic nervous system, where increased concentrations of excitatory neurohormones lead to peripheral vasoconstriction and increased heart rate. The kidneys may contribute to both the renal and neurohormonal mechanisms of hypertension. High sodium concentrations result in excess fluid retention by the kidneys, leading to increased intravascular volume and elevated blood pressure.

The kidneys may also contribute to neurohormonal mechanisms of hypertension through activity of the renin-angiotensin-aldosterone system (RAAS), which has some immediate effects on sodium and fluid retention but is also implicated in long-term changes to the vascular endothelium. Due in part to these alterations by the RAAS, the vascular mechanism of hypertension is characterized by an inability of vascular endothelial cells to appropriately respond to alterations in hemodynamics.

The pathologic outcomes of hypertension are primarily due to its deleterious effects on the microvasculature of target end-organs and the remodeling that may result from the body’s compensatory responses. Small blood vessels of the eyes, kidneys, brain, heart, and other end-organs...
are capable of sustaining temporary increases in blood pressure but are unable to withstand the chronic elevations characteristic of uncontrolled hypertension. Additionally, the remodeling that results from these chronic elevations leads to vascular fibrosis, where blood vessels become less capable of responding to systemic hemodynamic changes. Together, these pathologic changes in the vasculature often augment the effects of atherosclerosis in patients with CVD.

**Clinical Evaluation of Blood Pressure**

*Definitions*

In 2003, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) published guidelines to assist clinicians in the management of hypertension [1]. In response to emerging data indicating increased CVD risk even at blood pressures below 140/90 mmHg, the authors of JNC 7 developed a new classification known as prehypertension (defined as SBP 120-139 mmHg or DBP 80-89 mmHg) to identify patients at-risk for developing hypertension and in whom lifestyle modification might be beneficial in preventing the disorder. Pharmacotherapy is only recommended for patients with prehypertension in the presence of additional CVD risk factors (e.g., diabetes) and who fail a trial of lifestyle modifications. The remaining categories and their corresponding blood pressure values are shown in Table 2. For both Stage 1 and Stage 2 hypertension, guidelines recommend initiating medication therapy in addition to lifestyle modifications.

<table>
<thead>
<tr>
<th>Table 2. Blood Pressure Classifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure Classification</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Prehypertension</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
</tr>
</tbody>
</table>

Adapted from JNC 7 Guidelines (Reference 1)

*Preparing for Blood Pressure Measurements*

While automated devices have gained popularity, the gold standard for measuring blood pressure is the sphygmomanometer (i.e., inflatable cuff with an attached pressure gauge) and stethoscope. Blood pressure is traditionally measured at the site of the brachial artery, with the cuff positioned just above the crease of the elbow. Variation in arterial pressure by location is common, highlighting the importance of consistency when performing serial readings. Wrist monitors are fairly accurate when positioned at heart level, but these devices have not been as extensively studied as brachial blood pressure devices. Finger monitors are inaccurate and should not be used [12].

Blood pressure readings should be based on the average of two or more appropriately measured readings during at least two visits (Table 3). Accuracy depends significantly on appropriateness of cuff size (Table 4). For

<table>
<thead>
<tr>
<th>Table 3. Recommended Patient Preparation for Blood Pressure Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the most accurate blood pressure, patients should be prepared according to the following measures:</td>
</tr>
<tr>
<td>• Seated comfortably for at least 5 minutes</td>
</tr>
<tr>
<td>• Legs uncrossed and feet on floor</td>
</tr>
<tr>
<td>• Clothing removed at area of cuff placement</td>
</tr>
<tr>
<td>• Arm placed at heart level</td>
</tr>
<tr>
<td>• Caffeine, exercise, and smoking avoided for at least 30 minutes prior to measurement</td>
</tr>
<tr>
<td>• Cuff bladder encircling at least 80% of the arm (see Table 4)</td>
</tr>
<tr>
<td>• Background noise minimized</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. Recommended Cuff Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm Circumference</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>22-26 cm</td>
</tr>
<tr>
<td>27-34 cm</td>
</tr>
<tr>
<td>35-44 cm</td>
</tr>
<tr>
<td>45-52 cm</td>
</tr>
</tbody>
</table>

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example, a cuff that is too large will result in a falsely low blood pressure measurement.

**Instructions for Measuring Blood Pressure** [13]

Prepare the patient appropriately and select an adequately sized cuff. (See Tables 3-4)

- Palpate the brachial artery in the antecubital fossa (i.e., located slightly median to the dip of the inner elbow).
- Place the midline of the cuff bladder over the brachial artery about 2-3 cm above the antecubital fossa to allow room for stethoscope placement.
- The cuff should be inflated to at least 30 mmHg above the point at which the radial pulse disappears. (i.e., palpate the radial pulse and begin inflating the cuff; when the pulse disappears, note this value and inflate the cuff for an additional 30 mmHg)
- Place the stethoscope over the brachial artery. The bell of the stethoscope is usually better for auscultating Korotkoff sounds. Korotkoff sounds may resemble the *lub-dub* sound of heart chambers, but actually reflect the audible turbulence of blood flow into an artery when the cuff pressure drops below arterial blood pressure.
- With the stethoscope in place, deflate the cuff at a rate no faster than 2-3 mmHg per second.
- The SBP value is the point at which the first of two or more Korotkoff sounds is heard.
- The DBP value is the point at which the Korotkoff sounds disappear.
- Record both values and provide them to the patient in written and verbal form.

Multiple blood pressure measurements are of greater clinical value than an isolated reading. When taking multiple measurements, use the following steps:

- Wait at least 1-2 minutes between readings.
- Average multiple readings together for a more accurate representation of blood pressure.
- If two readings differ by more than 5 mmHg, obtain additional readings and determine an average blood pressure.
Goals of Therapy [1]
The primary objective of managing hypertension is to prevent end-organ damage and reduce global cardiovascular risk. Although some controversy remains as to the appropriate target of antihypertensive therapy, achievement of goal SBP remains the most commonly used clinical strategy. For most patients being treated for hypertension, goal BP is < 140/90 mmHg, as this value has been associated with a reduction in adverse CVD outcomes [2-3, 14]. For patients with diabetes or chronic kidney disease, the goal blood pressure is < 130/80 mmHg [15, 16]. Some clinicians may choose to target lower blood pressures in specific patients, citing the risk of cardiovascular events seen at blood pressures as low as 115/75 mmHg [3]. Although targeting lower blood pressures may reduce CVD risk, it may also increase the risk of hypotension (low blood pressure), which must be appropriately evaluated in each individual patient.

Management [1]
An algorithm for the prevention and management of hypertension is shown in Figure 1. Therapeutic lifestyle modifications should be recommended for all patients with prehypertension or hypertension. Lifestyle modifications demonstrated as being effective in the management of hypertension are weight reduction, adopting the Dietary Approaches to Stop Hypertension (DASH) diet, dietary sodium restriction, regular physical activity, and moderation of alcohol consumption. Details on these changes and their expected impact on SBP are shown in Table 5 (for additional details on non-pharmacologic approaches to reduce CVD risk, see module on lifestyle modifications). Finally, smoking cessation also provides benefit across the spectrum of CVD, including hypertension.

**Table 5. Lifestyle Modifications in Hypertension**
*Adapted from JNC 7 [1]*

<table>
<thead>
<tr>
<th>Activity</th>
<th>Goal</th>
<th>Reduction in SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Normal body weight (body mass index 18.5 – 24.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>kg/m²)</td>
<td>5 – 20 mmHg</td>
</tr>
<tr>
<td></td>
<td>(for every 10 kg lost)</td>
<td></td>
</tr>
<tr>
<td>Adopt DASH Eating Plan</td>
<td>Consume a diet rich in fruits and vegetables and</td>
<td>8 – 14 mmHg</td>
</tr>
<tr>
<td></td>
<td>low in saturated fat</td>
<td></td>
</tr>
<tr>
<td>Dietary sodium restriction</td>
<td>Reduce dietary intake to &lt; 2.3 g per day; &lt; 1.5 g</td>
<td>2 – 8 mmHg</td>
</tr>
<tr>
<td></td>
<td>per day has even greater benefit</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in aerobic activity at least 30 minutes per</td>
<td>4 – 9 mmHg</td>
</tr>
<tr>
<td></td>
<td>day on most days of the week</td>
<td></td>
</tr>
<tr>
<td>Moderation of alcohol</td>
<td>No more than 2 drinks per day in men and no more</td>
<td>2 – 4 mmHg</td>
</tr>
<tr>
<td>consumption</td>
<td>than 1 drink per day in women</td>
<td></td>
</tr>
</tbody>
</table>

Medication therapy is not indicated for patients with prehypertension in the absence of compelling CVD risk factors (e.g., diabetes); management should include an adequate trial of therapeutic lifestyle modifications aimed at preventing hypertension prior to the initiation of pharmacotherapy. Although
guidelines recommend initiating drug therapy for both stages of hypertension at diagnosis, some clinicians may opt for a short period of lifestyle modifications in specific patients. However, the vast majority of patients will receive drug therapy once hypertension has been diagnosed. The initial choice of medication therapy depends on the presence or absence of other compelling indications (i.e., other conditions where specific agents may have additional benefit independent of their effects on blood pressure). In the absence of compelling indications, a thiazide diuretic is generally recommended as first-line therapy, although this remains a subject of debate and may change with the publication of new guidelines.

Only a third of patients with hypertension are adequately controlled with monotherapy, so most will eventually require two or more antihypertensive medications. Because of the complex and variable mechanisms that cause or contribute to hypertension, a variety of treatment options exist. A list of common classes of antihypertensives can be found in Table 6.

**Hypertensive Crisis**

Blood pressure values exceeding 180/120 mmHg are known as hypertensive crises and can be classified as either hypertensive urgencies or emergencies. Hypertensive emergencies are differentiated from urgencies by the presence of end-organ damage, such as an intracranial hemorrhage or myocardial infarction. Emergencies require immediate blood pressure lowering, most commonly with intravenous agents. Both conditions should be considered medical emergencies and patients presenting with either should be referred to the nearest acute care facility.
References


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The emergence of cardiovascular disease (CVD) as the leading cause of worldwide mortality has been attributed to the growing incidence of unhealthy lifestyles among populations across the world. Although significant controversy surrounds the influence of specific dietary components on CVD risk, the factors thought to contribute most are diets high in saturated fats and sodium, and to a lesser extent carbohydrate consumption, combined with low levels of physical activity. As a result, obesity has reached epidemic proportions in many parts of the world, a trend that is expected to continue as rates grow among children and adolescents. In response to the health risks posed by increased rates of obesity across the country, the US Department of Health & Human Services recently published two sets of national guidelines, the 2010 Dietary Guidelines for Americans [1] and 2008 Physical Activity Guidelines for Americans [2].

This module reviews the most common lifestyle factors known to contribute to CVD risk, including obesity, diet, and physical inactivity. Although an unhealthy diet and sedentary lifestyle contribute to obesity, all three are independent risk factors for CVD. In addition to reviewing how these lifestyle factors contribute to adverse cardiovascular outcomes, the following section also summarizes strategies associated with reductions in CVD risk.

Definitions for Excess Body Weight & Obesity

Body weight is often described in terms of body mass index (BMI), calculated as weight in kilograms divided by height in meters squared (kg/m²). Based on BMI, patients can be classified as underweight, normal, overweight, or obese (Table 1). Several calculators are available to help determine BMI, including one published by the US National Institutes of Health (NIH) at: http://www.nhlbisupport.com/bmi/.

<table>
<thead>
<tr>
<th>Table 1. Body Mass Index Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>US National Institutes of Health (NIH)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>&lt;18.5</td>
</tr>
<tr>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td>25.0 – 29.9</td>
</tr>
<tr>
<td>&gt;30</td>
</tr>
</tbody>
</table>

Epidemiology of Obesity

Over the past 20 years, the prevalence of obesity in the US has doubled [3]. Two-thirds of American adults are overweight and one-third are obese [4]. One-third of children are above the 85th percentile for age-adjusted BMI [4], making them 70% more likely to become overweight as adults [5]. Based on these trends, some experts estimate that by 2030, over 80% of adults will be overweight and half will be obese [6].

In 2000, an estimated 112,000 excess deaths were attributed to obesity [7]. While being overweight (i.e., BMI 25.0 – 29.9) does not appear to contribute to cardiovascular mortality, the risk of death increases significantly at BMIs >30 [8]. On average, overweight adults live approximately 3 years less than those of normal body weight, while the lifespan of obese adults are between 5 and 7 years shorter [9].

Many attribute the increased risk of CVD to diet and physical inactivity alone. However, excess weight appears to increase risks independent of dietary content or level of physical activity [10]. The risk of developing CVD is increased by approximately 20% among adults who are overweight and between 46% and 64% for adults who are obese [11].

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Goals
According to guidelines published by the NIH, the goal for adult patients is to achieve and maintain a body weight that optimizes health, a strategy which allows individuals to customize their approach to weight loss according to criteria appropriate for age, gender, caloric needs, and a variety of other characteristics (e.g., pregnancy, chronic medical conditions). Key strategies for addressing these goals are eating fewer calories and choosing healthier nutritive options while increasing physical activity. Independent of their impact on weight loss, these strategies also improve health outcomes in patients of normal weight.

Dietary Modifications
Both the absolute number of calories consumed and the specific content of one’s diet can contribute to CVD risk. At the most fundamental level, weight is maintained when energy intake equals energy output. Energy intake is determined by calories consumed while energy output is a function of resting metabolic rate and physical activity. A third contributor to energy consumption is the thermic effect of food, a term used to describe the temporary increase in energy consumption required to digest, absorb, use and store food. When calories consumed exceed those expended, excess energy is stored as fat. Similarly, weight is lost when energy expenditure exceeds calories consumed. The balance of energy intake and output contributes to body weight and as a result, the development of obesity.

Excess cardiovascular risk may also be imparted by the content of food. The two most common dietary targets related to CVD are sodium and fats (e.g., triglycerides and cholesterol), although increasing emphasis has been placed on the association of carbohydrate (i.e., sugar) consumption and CVD. Fats play an important role in the structure of cell membranes and in the biosynthesis of several endogenous hormones, but certain types also increase the risk for CVD. The fats contained in olive oil, nuts, and vegetables have been shown to improve cardiovascular outcomes, while others contribute to cardiovascular risk by increasing serum lipoproteins, especially low density lipoprotein (LDL) and total cholesterol, two parameters strongly correlated with cardiovascular morbidity and mortality.

Saturated fats, commonly found in meats and dairy products, are the most significant contributor to total cholesterol and LDL. Recently, significant attention has also been placed on trans fats, which are produced by the chemical modification of unsaturated fatty acids in order to increase their stability. Recent legislation by the US Food & Drug Administration (FDA) requires manufacturers to list trans fat content alongside other types of fat in food product labeling.

The second target for reducing CVD risk is sodium content. Like fats, sodium also plays several important physiologic roles, including the maintenance of fluid balance. When excess sodium is consumed, the body compensates by retaining fluid, which can significantly increase blood pressure. As explained in the section to follow, sodium restriction can have a profound effect on blood pressure and serves as one strategy for reducing cardiovascular risk.

Finally, certain types of carbohydrates have also been associated with CVD risk, although significant controversy surrounds whether these risks are associated with all carbohydrates or specific types (i.e., simple versus complex), or are due to their conversion of excess carbohydrates to fats or contribution to the rates of diabetes mellitus. A detailed discussion of this topic is beyond the scope of these materials, thus coverage will be limited to the recommendations listed in current guidelines.
Evidence for the Benefits of Dietary Modification
The benefits of dietary modification have been shown in several large epidemiologic investigations. For example, a meta-analysis of prospective cohort studies demonstrated that consumption of whole grains may reduce the risk of CVD by as much as 21% [12]. Additionally, increased intake of fruits and vegetables decreases the risk of coronary artery disease and stroke by 4% and 5%, respectively [13, 14]. Finally, post-hoc analysis of the Trials of Hypertension Prevention (TOHP) study demonstrated that lower sodium intake was associated with a 25% lower incidence of CVD, even up to 15 years after study enrollment [15].

Two prospective studies [16, 17] serve as the basis for the Dietary Approaches to Stop Hypertension (DASH) Eating Plan [18], a strategy shown to reduce blood pressure in both hypertensive and normotensive patients. In the first DASH study [16], patients randomized to diets high in fruits and vegetables and low in fat had statistically significant reductions in blood pressure. The second DASH trial [17] randomized patients to diets of varying levels of sodium content and showed that reductions in dietary sodium can significantly improve blood pressure. Furthermore, the study showed that the incorporation of other healthy components into one's diet can reduce blood pressure to levels even lower than sodium reduction alone.

Recently, the Prevención con Dieta Mediterránea (PREDIMED) study demonstrated a reduction in cardiovascular events among patients at high risk for CVD who were randomized to a Mediterranean diet supplemented with olive oil or nuts [19]. Patients randomized to a Mediterranean diet were encouraged to eat olive oil, nuts, fresh fruits, vegetables, and lean white meats, while patients in the control arm were encouraged to eat a reduced-fat diet. After a median of nearly 5 years, a 30% relative reduction in major adverse cardiovascular events (i.e., the composite of myocardial infarction, stroke, or death from cardiovascular events) was observed in the Mediterranean diet group.

Management Strategies
To promote health and prevent the development of chronic disease (including CVD), an advisory board representing the US Department of Agriculture and US Department of Health & Human Services published the 2010 Dietary Guidelines for Americans [1]. Although a variety of “heart healthy” diets exist in popular literature, these guidelines will serve as the focus for this module. A summary of key recommendations will be reviewed here, but for more information, readers are referred to the complete guidelines available online at http://www.health.gov/dietaryguidelines/.


General Recommendations
Guidelines recommend a balanced diet consisting of nutrient-rich foods in each of the basic food groups and limited intake of fats, cholesterol, added sugars, sodium, and alcohol. Calorie goals should be individualized to maintain body weight within a healthy range. An example of nutrient content based on a 2100 calorie diet is shown in Table 2. Examples of specific serving sizes and serving numbers are shown in Table 3.
**Fruits, Vegetables, Grains, and other Carbohydrates**
A diet rich in fruits and vegetables is highly recommended. A diverse assortment should be chosen each day and specific serving numbers and sizes should be based on caloric needs. Half of total grain intake should come from whole grains and fiber-rich foods should be chosen when possible. Prepared foods should contain as little added sugar as possible.

**Meat & Dairy Products**
For meat and dairy products, the guidelines recommend selecting lean, low-fat, or fat-free varieties.

**Fats**
In general, total fat intake should range between 20% and 35% of total calories. Oils and fats high in saturated or trans fatty acids should be limited. If possible, most fats should be derived from polyunsaturated and monounsaturated fatty acids. For most Americans, the guidelines recommend that less than 10% of total calories come from saturated fatty acids. For patients who have hypertension or are at risk for CVD, the DASH Eating Plan suggests more aggressive fat goals (less than 6% of total calorie intake) [18], although sources of fats associated with improved outcomes as part of a Mediterranean diet (i.e., olive oil, nuts) may be encouraged [19].

**Sodium & Potassium**
For most Americans, sodium should be restricted to less than 2300 mg (1 teaspoonful) per day. For patients with high blood pressure or those who are at high risk for CVD, a goal of 1500 mg of sodium per day may be considered, although a recent report by the Institute of Medicine challenged sodium goals < 2300 mg per day after failing to find conclusive evidence of benefit [20]. Although the second DASH trial indicated a lower sodium target (< 1200 mg) was associated with the most significant reduction in blood pressure [17], sodium consumption that is too low may also pose health risks [20]. Foods rich in potassium (e.g., fruits and vegetables) are also recommended.

<table>
<thead>
<tr>
<th>Table 2. Daily Nutrient Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Based on a 2100 calorie eating plan)</td>
</tr>
<tr>
<td>Carbohydrate</td>
</tr>
<tr>
<td>Protein</td>
</tr>
<tr>
<td>Total fat</td>
</tr>
<tr>
<td>Saturated fat</td>
</tr>
<tr>
<td>Cholesterol</td>
</tr>
<tr>
<td>Sodium</td>
</tr>
<tr>
<td>Potassium</td>
</tr>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>Fiber</td>
</tr>
</tbody>
</table>

\(^*\) Daily sodium goals of < 1500 mg demonstrated even greater reductions in blood pressure and may be recommended in high-risk patients or those with established cardiovascular disease.

<table>
<thead>
<tr>
<th>Table 3. DASH Eating Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food Group</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Grains(^3)</td>
</tr>
<tr>
<td>Vegetables</td>
</tr>
<tr>
<td>Fruits</td>
</tr>
<tr>
<td>Fat-free or low-fat dairy products</td>
</tr>
</tbody>
</table>

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Lean meats, poultry, and fish | 6 or less | 1 oz cooked meats, poultry, or fish | 1 egg
Nuts, seeds, and legumes | 4 – 5 per week | 1/3 cup or 1 1/2 oz nuts | 2 tbsp peanut butter | 2 tbsp or 1/2 oz seeds | 1/2 cup cooked legumes (dry beans and peas)
Fats and oils | 2 – 3 | 1 tsp soft margarine | 1 tsp vegetable oil | 1 tbsp mayonnaise | 2 tbsp salad dressing
Sweets and added sugars | 5 or less per week | 1 tbsp sugar | 1 tbsp jelly or jam | 1/2 cup sorbet, gelatin | 1 cup lemonade

Adapted from the DASH Eating Plan [18]
1 Whole grains recommended
2 Serving sizes may differ based on specific type of cereal
3 Eggs are high in cholesterol, so limiting egg yolk consumption is recommended
4 Specific fat content changes the serving amount for fat and oils; consult nutrition labeling for more information

More Information on Fat Intake
According to clinical guidelines for the management of hyperlipidemia published by the National Cholesterol Education Panel (NCEP), therapeutic lifestyle changes are recommended as an important strategy for reducing cardiovascular risk [10]. Many of their recommendations overlap those of the DASH Eating Plan, so focus here will be placed primarily on the additional detail the NCEP guidelines provide on dietary fat content.

In general, the NCEP guidelines recommend reduced dietary intake of saturated fat and cholesterol combined with increased intake of foods known to lower LDL and reduce cardiovascular risk (Table 4). For example, saturated fat should comprise < 7% of total calories per day. Additionally, 2 g of plant sterol or stanol esters should be consumed daily to enhance lowering of LDL.

The guidelines also discuss the benefits of dietary supplementation with omega-3 fatty acids, such as those found in fish oil, which have been shown to improve hyperlipidemia and reduce the risk of CVD [21]. While the potential mechanism for their benefit is not clear at this time, modest consumption of fish oils (< 1 g/day) has been associated with decreased cardiovascular risk while larger amounts (4 – 6 g/day or more) improve LDL, high density lipoprotein (HDL), and triglycerides [22]. Recent evidence has challenged the consumption of fish oil in patients

Table 4. Nutrient Composition of TLC Diet

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fat</td>
<td>&lt; 7% of total calories</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>Up to 10% total calories</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>Up to 20% total calories</td>
</tr>
<tr>
<td>Total fat</td>
<td>25 – 35% of total calories</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>50 – 60% of total calories</td>
</tr>
<tr>
<td>Fiber</td>
<td>20 – 30 g/day</td>
</tr>
<tr>
<td>Protein</td>
<td>Approximately 15% of total calories</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt; 200 mg/day</td>
</tr>
<tr>
<td>Total calories (energy)</td>
<td>Balance intake and expenditure to maintain desirable body weight and prevent weight gain</td>
</tr>
</tbody>
</table>

Adapted from the National Cholesterol Education Panel guidelines on the management of high blood

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without established CVD (e.g., history myocardial infarction) or heart failure, as a prospective study of its use in high-risk patients failed to demonstrate a benefit [23]. Currently, the American Heart Association recommends that adults consume at least two servings of fish per week, although some caution should be given to consuming excessive amounts of fish, as this may increase exposure to methylmercury and other environmental contaminants [24]. Fish oil supplements do not contain methylmercury and have been deemed safe for consumption.

**Alcohol Consumption**

Numerous epidemiologic investigations have suggested an association between moderate alcohol consumption and improved health outcomes, including a reduction in CVD risk. The relationship between alcohol consumption and total mortality is commonly described in terms of a *J-shaped curve*, where mortality is reduced at moderate levels of consumption but returns to baseline and eventually increases at higher levels of consumption. While moderate consumption is associated with reduced incidence of coronary artery disease and overall mortality, excessive alcohol consumption increases the incidence of several cardiovascular disorders, including hypertension and cardiomyopathy. As a result of these trends and the risk for alcohol addiction, consumption is not “prescribed” for patients who do not currently drink. Instead, recommendations are aimed at patients who already consume alcohol.

Definitions for alcohol consumption and the volume constituting one drink varies widely in the literature. The terms used in this module are consistent with the 2010 *Dietary Guidelines for Americans* [1], which define moderate consumption as up to one drink per day for women and up to two drinks per day for men. Specific volumes by type of beverage are listed in Table 5.

**Beneficial Effects of Alcohol Consumption**

A recent meta-analysis published in the *Archives of Internal Medicine* examined over 30 prospective studies and confirmed the *J*-shaped curve suggested by previous analyses [25]. Consumption of alcohol was inversely related to total mortality for up to 2 drinks per day for women and up to 4 drinks per day for men. Above these thresholds, total mortality was higher than baseline risk. Overall, mortality was reduced by a maximum of 18% in women and 17% in men and the greatest reductions occurred at about one-half drink per day.

Several other studies have found similar results with regards to total mortality [26-28] and cardiovascular morbidity and mortality [29, 30]. Some controversy exists as to whether cardiovascular risk reduction occurs with all types of alcoholic beverages or only specific varieties. While some studies have shown more significant effects with red wine versus other types of alcohol, these have not been confirmed in all investigations [30].

The differential response among men and women has been attributed to several factors, although none have been fully elucidated. On average, women are exposed to higher concentrations of alcohol per drink due to decreased activity of alcohol dehydrogenase, an enzyme responsible for alcohol metabolism. Other possible explanations include the fact that women are already at lower risk for the development of coronary artery disease and other types of CVD when compared to men.

### Table 5. Serving Sizes of Alcoholic Beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Serving Volume</th>
<th>Percent alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>12 fl oz</td>
<td>5%</td>
</tr>
<tr>
<td>Wine</td>
<td>5 fl oz</td>
<td>12%</td>
</tr>
<tr>
<td>Liquor</td>
<td>1.5 fl oz</td>
<td>40%</td>
</tr>
</tbody>
</table>

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The underlying mechanisms for reduced CVD risk are not clear at this time but are likely multifactorial. Alcohol consumption has been shown to increase HDL cholesterol [31], which is considered a negative risk factor for the development of coronary artery disease. Alcohol has also been shown to reduce plasma viscosity and platelet aggregation [32], which may reduce the risk of myocardial infarction or stroke. Finally, alcohol may reduce atherosclerosis, as demonstrated in patients undergoing coronary angiography who consumed alcohol compared to those who did not [33].

While alcohol consumption has been linked to improved cardiovascular outcomes, these benefits exist only at the levels of moderate consumption. At higher amounts, alcohol contributes to excess cardiovascular risk, especially for patients who drink heavily or engage in binge drinking (irregular episodes of excess alcohol consumption) [34]. Alcohol consumption is also problematic in patients with specific underlying medical conditions, such as liver diseases, hypertension, and hypertriglyceridemia.

Management Strategies
The beneficial relationship between moderate alcohol consumption, cardiovascular risk, and total mortality is primarily based on epidemiologic evidence. In the absence of large randomized controlled trials, it is inappropriate at this time to recommend alcohol consumption to patients who currently do not drink. However, for the 55% of Americans who do currently consume alcohol, clear recommendations can be made.

Those who choose to drink alcohol should do so in moderation, defined as up to one drink per day in women and up to two drinks per day in men. Evidence indicates that total mortality is reduced at up to 2 and 4 drinks for women and men respectively; however, the greatest benefit is seen at about half a drink per day and remains relatively stable at 1 and 2 drinks for women and men, respectively. Consuming alcohol in excess of these recommendations has been shown to contribute both to cardiovascular and overall mortality.

Alcohol should still be avoided by certain patient groups, including women who are pregnant or who may become pregnant, children and adolescents, patients with certain medical conditions or who take medications that interact with alcohol, and for people engaging in activities that require skill or concentration (e.g., driving or operating heavy machinery).

Physical Activity
The rising rates of obesity across the US have also been attributed to an increasingly sedentary lifestyle among most Americans. A quarter of Americans report no leisure-related physical activity and a tenth report no moderate-to-vigorous physical activity of any type [35, 36]; these rates exceed 59% when only vigorous activities are considered [37].

While physical inactivity may increase cardiovascular risk by contributing to obesity, it is also independently associated with poor cardiovascular outcomes. In fact, evidence indicates that the increased risks associated with physical inactivity are comparable to those of traditional risk factors, including hyperlipidemia, hypertension, and tobacco use [38]. As a result, the US Department of Health & Human Services recommends in the 2008 Physical Activity Guidelines for Americans that all Americans engage in regular physical activity in order to improve overall health and prevent disease.

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The guidelines define physical activity as any bodily movement that enhances health when added to baseline daily activities. Examples cited include running or jogging, playing sports, lifting weights, swimming, dancing, and performing yoga. These activities differ from activities of daily living, which may include walking, standing, or periodic episodes of moderate-to-vigorous activity, such as lifting heavy objects or climbing several sets of stairs. Although exercise (i.e., routine, scheduled physical activity) is the most commonly recommended form of physical activity, the guidelines recognize that physical activity may come in a variety of forms. They also recognize that some adults may meet recommended levels of physical activity based on job function (e.g., construction workers, shipping and delivery personnel).

Evidence for the Benefits of Physical Activity
Decades of research have demonstrated the health benefits of physical activity, which may be seen with as little as 60 minutes of physical activity per week. However, the greatest benefit appears to occur at a total amount of 150 minutes of moderate-intensity aerobic activity per week [2]. Based on a review of the literature, the authors of the 2008 guidelines assign specific levels of evidence to the benefits physical activity imparts to a variety of medical conditions. Of the conditions with the highest-rated level of evidence (“strong evidence”), many are cardiovascular disorders, including coronary artery disease, stroke, hypertension, and hyperlipidemia. Other key findings are listed in Table 6.

Management Strategies
A summary of key recommendations from the 2008 Physical Activity Guidelines for Americans will be reviewed here; for details and additional information on specific patient populations, complete guidelines can be accessed online at http://www.health.gov/paguidelines/.

The guidelines identify four levels of moderate-intensity physical activity based on number of minutes per week: inactive, low, medium, and high (see Table 7 and 8).

<table>
<thead>
<tr>
<th>Table 6. Summary of Health Benefits of Physical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Regular physical activity improves health outcomes in all patients</td>
</tr>
<tr>
<td>- Some physical activity is better than none, but outcomes are improved with higher intensities, greater frequencies, and/or longer durations</td>
</tr>
<tr>
<td>- Most benefits occur with &gt; 150 minutes/week of moderate-intensity physical activity</td>
</tr>
<tr>
<td>- Health benefits seen children, adolescents, adults, and older adults</td>
</tr>
</tbody>
</table>

Adapted from the 2008 Physical Activity Guidelines for Americans [2]

<table>
<thead>
<tr>
<th>Table 7. Classification of Total Weekly Amounts of Aerobic Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of Physical Activity</strong></td>
</tr>
<tr>
<td>Inactive</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Medium</td>
</tr>
<tr>
<td>High</td>
</tr>
</tbody>
</table>

Adapted from the 2008 Physical Activity Guidelines for Americans [2]
The guidelines recommend that all adults avoid inactivity. While some physical activity is better than none, additional health benefits are seen at higher levels of physical activity. To obtain the minimum health benefits of physical activity, adults should obtain at least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity physical activity (a list of example moderate- and vigorous-intensity activities are provided in Table 8). To maximize health benefits, the amount of physical activity should be performed daily when possible. Consistent with the 2010 Dietary Guidelines for Americans [1], adults should engage in at least 60 minutes of moderate- to vigorous-intensity physical activity on most days of the week in order to maintain body weight and prevent gradual weight gain; 60-90 minutes should be performed in order to lose weight. Weight-strengthening activities are also recommended for adults seeking additional health benefits.

Recommendations for physical activity may be different for specific patient populations. For example, children should engage in higher levels of physical activity than adults; currently 60 minutes or more per day are recommended. Pregnant women are advised to engage in 30 minutes of moderate-intensity physical activity per week. For older adults, physical activity continues to provide health benefits but activities should be based on maximizing health benefits while minimizing the risk of injury.
References


According to recent estimates, nearly 1 in 5 Americans smoke cigarettes [1]. Although rates of tobacco use have declined since the 1960s, this trend has slowed significantly over the last decade and cigarette smoking remains the leading preventable cause of death in the United States [1-3]. Cigarette smoking and other forms of tobacco can cause or contribute to a number of disorders, including cancer, pulmonary disease, and cardiovascular disease (CVD). In response to the significant morbidity and mortality associated with tobacco use, the US Public Health Service (USPHS) issued guidelines to assist health care providers in identifying and managing patients who use tobacco products.

The profession of pharmacy has maintained strong opposition to cigarettes and other tobacco products. The first policy discouraging sale of tobacco in pharmacies was adopted by the American Pharmacists Association (APhA) in 1968 and was reaffirmed as recently as 2010. Over the last several decades, pharmacists have also emerged as frontline providers of tobacco cessation education and assistance services. As the most accessible health care professionals, pharmacists are ideally positioned to support and assist patients in their efforts to quit using tobacco products [4, 5]. Evidence also indicates that pharmacist-assisted intervention strategies improve success rates [6]. Student pharmacists can support these efforts by identifying tobacco users in the community, educating them on the benefits of cessation, and referring them to health care providers who can assist with a quit attempt.

Most of the evidence linking tobacco use to CVD has been the result of investigations involving cigarette smoking. However, CVD risks have also been linked to smokeless tobacco products. While this module focuses primarily on smoking cessation, abstinence from any form of tobacco can effectively reduce the risk of CVD.

**Smoking & Tobacco Use as a Risk Factor for Cardiovascular Disease**

Cigarette smoking has been associated with an increased risk of several cardiovascular disorders, including angina, myocardial infarction, stroke, peripheral vascular disease, and sudden cardiac death [1, 2]. For patients with established coronary artery disease (CAD), cigarette smoking is also an independent predictor of cardiac arrest [7]. Second-hand exposure to cigarette smoke may also increase one’s risk of CAD. Some estimates indicate that non-smokers exposed to second-hand smoke have at least a 25-30% increased risk of CAD, while others indicate the risks are up to 80-90% of those found in active smokers [8].

Patients who quit smoking can drastically reduce their cardiovascular risk. According to one estimate, patients with CAD who quit smoking can reduce their risk to a level comparable to healthy non-smokers within 3 years [9]. For patients without CAD, the benefits are also dramatic – within one year of quitting, former smokers reduce their CAD risk by half, and excess risks may be completely eliminated within 5 – 15 years [10].

**Epidemiology**

Despite aggressive public awareness campaigns highlighting the detrimental effects of tobacco use and secondhand exposure, cigarette smoking remains the primary cause of death for nearly 440,000 Americans each year [1]. A third of these deaths are related to CVD and a tenth of all smoking-related deaths can be attributed to secondhand smoke [1, 11].
The prevalence of smoking has declined by approximately 50% over the last four decades [12] but 1 in 5 Americans continue to smoke and another 8 million use smokeless tobacco products [1, 13]. The rate of new smokers has steadied in recent years; 2.2 million Americans smoked their first cigarette in 2007, representing an average of over 6000 new smokers each day [13]. Unfortunately, this trend begins early in life, as most report smoking their first cigarette at 14-15 years of age [3]. In fact, the prevalence of tobacco use is highest among young adults (age 18-25 years), where nearly 1 in 3 report cigarette smoking and 1 in 10 report use of smokeless tobacco products [3].

Cigarette smoking also places a significant financial burden on the US health care system. Between 2000 and 2004, medical and lost productivity costs associated with cigarette smoking exceeded $96 and $97 billion, respectively [1]. Health care for patients exposed to secondhand smoke represents an additional $10 billion in costs annually.

Etiology
The etiology of tobacco use can be attributed to the addictive properties of nicotine, a psychoactive substance that utilizes the same addiction pathway as alcohol, cocaine, and methamphetamines. Once absorbed into the blood stream, nicotine acts on receptors throughout the central and peripheral nervous systems. In the central nervous system (CNS), the addictive action of nicotine is a result of increased dopamine concentrations, which stimulate the mesolimbic pathway of the midbrain (often called the reward circuit) and elicit feelings of relaxation or euphoria. Over time, these pathways are responsible for reinforcing habitual use of the drug. Evidence also indicates that tobacco smoke may contain substances that inhibit the breakdown of active neurotransmitters (including dopamine), which could further contribute to the psychoactive effects of nicotine [14].

The addictive properties of nicotine also include its tendency to promote compulsive use (often in progressively increasing doses) and its association with behavioral or environmental factors that reinforce continued use. Many smokers associate cigarette smoking with certain environments or activities (e.g., driving, drinking alcohol), which may serve as “triggers” for the reward pathway. As addiction progresses, smoking in these situations becomes habitual and difficult to manage even when patients make the decision to quit.

Pathophysiology
The pathophysiology of cigarette smoking is primarily due to the presence of (1) nicotine, and (2) the diverse assortment of compounds found in cigarette smoke and particulate matter (commonly referred to as “tar”), many of which are known carcinogens. As a result of the processes involved in growing and preparing tobacco, smokeless tobacco products retain many of the carcinogens found in cigarettes [15], while nicotine content differs according to product (See Table 1).

Table 1. Nicotine Content of Selected Tobacco Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Nicotine Content (mg/g tobacco)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes</td>
<td>13.7 – 23.18</td>
</tr>
<tr>
<td>Chewing tobacco</td>
<td>3.41 – 39.74 (mean 9.9)</td>
</tr>
<tr>
<td>Dry snuff</td>
<td>10.48 – 24.84 (mean 16.8)</td>
</tr>
<tr>
<td>Moist snuff</td>
<td>4.7 – 24.29 (mean 12.6)</td>
</tr>
</tbody>
</table>

According to a review by Ludvig, et al, smoking is thought to increase cardiovascular risk via four mechanisms [16]; namely, it:

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• Induces a hypercoagulable state by activating platelets and promoting the coagulation cascade;
• Increases the concentration of carbon monoxide, which binds to hemoglobin and reduces the number of sites available for oxygen transport;
• Causes coronary vasoconstriction, reducing coronary blood flow and increasing the risk of vasospasm; and,
• Exposes vascular tissue to the pharmacodynamic effects of nicotine, which include acute increases in heart rate, blood pressure, oxygen demand, myocardial contractility, and coronary vasoconstriction.

Cigarette smoking also contributes to endothelial atherosclerosis, which can further predispose patients to the development of CAD or worsens outcomes in those with established disease [16].

Clinical Evaluation
Tobacco smokers may present differently based on length of smoking history, time since last cigarette smoked, and the presence or absence of other comorbid conditions (e.g., chronic obstructive pulmonary disease, asthma). Most patients who have recently smoked (i.e., within 15 – 30 minutes) will present with elevated blood pressure and heart rate, while others may become attenuated to these effects over time. Even if patients no longer respond to the hemodynamic effects of nicotine, cigarette smoking continues to contribute to the underlying inflammatory processes responsible for CAD.

For student pharmacists interacting with patients in the community, it may also be important to recognize the signs and symptoms of nicotine withdrawal, which often peak at 48 hours after cessation of tobacco use [17]. The most troubling symptoms are related to reduced concentrations of nicotine in the CNS, including feelings of anxiety or depression, irritability, restlessness, drowsiness or insomnia, headaches, and intense cravings. While nicotine withdrawal may have only mild effects on hemodynamics, patients may experience elevations in blood pressure or heart rate secondary to anxiety, irritability, or other psychological symptoms associated with nicotine withdrawal. Most withdrawal symptoms gradually disappear over a period of several weeks, although increased appetite and weight gain may remain for months [17].

Goals of Therapy
The primary goal of therapy is abstinence from tobacco use, although this may oversimplify the often complex strategies necessary to ensure a successful quit attempt. As described above, tobacco use is accompanied by a powerful addictive pathway that can make quitting difficult. While 70% of cigarette smokers would like to quit, less than 5% are able to maintain abstinence for up to a year [18]. A multidisciplinary approach and a combination of behavioral and pharmacologic strategies can significantly increase a patient’s odds of quitting [2].

Clinician-assisted strategies for tobacco cessation are diverse and multifaceted. The following section describes some of these strategies in brief, but for complete detail, readers are referred to the 2008 Treating Tobacco Use and Dependence guidelines published by the USPHS Office of the Surgeon General (http://www.surgeongeneral.gov/tobacco/) [2]. A summary of these and other recommendations for management may also be found in the Smoking Cessation chapter in APhA’s Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care (17th ed) [17].

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Management
As outlined in national guidelines, smokers and other tobacco users should receive an intervention at every health care visit. Patients identified as smokers or tobacco users should be advised to quit and offered clinically-appropriate management or referral to a trained provider. Even interventions as brief as 3 minutes can improve the success rate of cessation strategies, while advanced sessions increase these rates even further [1]. Intervention by a pharmacist may increase the likelihood of quitting by as much as 1.7 times that of patients who receive no intervention at all [1].

Management strategies begin with identifying and appropriately assessing patients who currently smoke or use tobacco products. One of the most common paradigms for this process (also known as the “5 A’s”) is to (1) ask patients about tobacco use; (2) advise them to quit; (3) assess their willingness to make a quit attempt; (4) assist in the quit attempt; and (5) arrange for follow-up.

Ask
Patients should be asked if they use tobacco products at every health care visit. In addition to identifying a patient’s risk for smoking-related health outcomes, asking about tobacco use may assist with other clinical evaluations. Tobacco products may interact with medication therapy or interfere with blood pressure or heart rate measurements. A positive smoking or tobacco history should be documented in a patient’s medical record and include the type of product used (e.g., cigarettes, smokeless tobacco), frequency of use, and duration of use.

Advise
Tobacco users should be counseled on the risks of continued use and the benefits of cessation. Clinicians who advise patients should do so in a manner that is clear and strong but is personalized and demonstrates concern for the patient’s health and well-being [1]. Messages should connect a patient’s individual health status with the use of tobacco products, especially for patients who already have documented cardiovascular or pulmonary disease [17]. Because successful tobacco cessation requires behavioral modification, motivational interviewing can be a critical step in encouraging patients to quit.

Assess
After urging patients to quit tobacco use, further management is based on an assessment of the patient’s willingness to quit. Patients who are unwilling to quit should still be managed with strategies that may increase their chances of quitting in the future. Motivational interviewing may provide tobacco users with incentives to quit. Additionally, patients who are unwilling to quit may benefit from the “5 R’s” [19]: relevance of quitting; risks to themselves, friends, or family; rewards associated with quitting; roadblocks to quitting; and by repeating these strategies at every visit.

Assist
Patients who are willing to quit should be offered an assistance plan that includes behavioral strategies and if clinically appropriate, pharmacologic therapy. Many state health departments and professional organizations provide tobacco cessation programs, including in-person counseling sessions or toll-free telephone support lines. For patients with limited options locally, the federal government provides a free tobacco cessation resource online at smokefree.gov or 1-800-QUIT-NOW.

Pharmacists are ideally positioned to assist patients in the development of an individualized management plan, including the selection of appropriate tobacco cessation products. Patients should
understand that medications can significantly increase their chances of quitting successfully. Although some individuals may be reluctant to try pharmacologic therapy based on financial limitations, continued tobacco use generally exceeds that of most therapies. For example, cigarettes often exceed $5 per pack on average [20], while many nicotine replacement products may cost only a few dollars per day or less.

Currently, seven medications are recommended by national guidelines as first-line options for increasing abstinence rates among tobacco users (Table 2) [1]. Five agents are forms of nicotine-replacement therapy (NRT), while two are non-nicotine containing agents (bupropion sustained-release [SR] and varenicline). Although most patients should be urged to incorporate pharmacotherapy into their overall management plan, some should be supervised by a health care provider prior to selecting therapy. One such indication is severe CVD, such as patients who have recently experienced an acute event. Once patients have been stabilized, however, the benefits of smoking cessation outweigh the risks of NRT therapy [21].

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Replacement Therapy (NRT)</td>
<td>Nicotine gum</td>
<td>Nonprescription</td>
</tr>
<tr>
<td></td>
<td>Nicotine lozenge</td>
<td>Nonprescription</td>
</tr>
<tr>
<td></td>
<td>Nicotine inhaler</td>
<td>Prescription only</td>
</tr>
<tr>
<td></td>
<td>Nicotine nasal spray</td>
<td>Prescription only</td>
</tr>
<tr>
<td></td>
<td>Nicotine patch</td>
<td>Nonprescription</td>
</tr>
<tr>
<td>Non-Nicotine Therapies</td>
<td>Bupropion sustained-release (SR)</td>
<td>Prescription only</td>
</tr>
<tr>
<td></td>
<td>Varenicline</td>
<td>Prescription only</td>
</tr>
</tbody>
</table>

Of the available smoking cessation therapies, the nicotine gum, lozenge, and transdermal patch are available as nonprescription products. The remaining agents are available by prescription only. Prescription nortriptyline and clonidine are also recognized by national guidelines as second-line agents to assist with tobacco cessation, although neither is approved by the FDA for this indication.

Few head-to-head trials compare tobacco cessation therapies, so choosing a specific agent is usually based on individual patient characteristics or personal preference. In one meta-analysis, the absolute increase in abstinence rates among patients using the nicotine gum, patch, inhaler, or bupropion SR was approximately 10%, representing a relative increase in quit rates of almost twice that of placebo [16]. Transdermal nicotine patches may be especially useful for patients with established CAD, as the formulation has been demonstrated as being safe and effective in this population [22]. Sustained-release bupropion is also safe and may even be more efficacious in maintaining abstinence [23, 24].

Combination NRT is effective in patients who are unable to successfully quit using one agent alone [1]. Because there are only limited safety and efficacy data on the use of combination therapy, the guidelines only recommend this strategy when patients have failed monotherapy. Recommended combinations include the nicotine patch combined with either the gum or nasal spray, as these regimens have been shown as being the most effective.
Varenicline is the first new agent for smoking cessation approved by the FDA in nearly a decade. At a total daily dose of 1 mg, varenicline has been shown to double the chances of smoking cessation; at doses of 2 mg, these chances are tripled compared to placebo [1]. Although the incidence remains controversial, there have been some reports of psychiatric disturbances in patients taking varenicline; as a result, the FDA has added a warning to the medication that calls for patients to discuss any history of psychiatric illness with their primary care provider and for all clinicians to observe for changes in mood or behavior in patients taking the agent.

Arrange
The final step in the management of clinician-assisted tobacco cessation is arranging for follow-up visits. As described previously, multiple interventions increase the chances of quitting. Thus, guidelines recommend scheduling a follow-up visit shortly after the established quit date and if possible, within the first week. Regardless of quit status, the goal of follow-up is to help patients identify challenges they have already encountered during their quit attempt and to assist them in anticipating roadblocks in the future. A second contact should be made within the month.
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The following section provides information on additional risk factors for cardiovascular disease (CVD) that have not been discussed in previous modules.

Diabetes

According to the US Centers for Disease Control and Prevention (CDC), nearly 26 million Americans (8.3%) have diabetes, of which 7 million remain undiagnosed [1]. About 1.9 million adults were diagnosed in 2009 and the incidence among both adults and adolescents appears to be growing each year. The primary cause of death in over two-thirds of patients with diabetes is CVD, where rates of CVD-related mortality are 2-4 times that of patients without diabetes [1]. Because of the strong association between diabetes and CVD, many consider diabetes a risk equivalent for coronary artery disease (CAD) [2].

Health outcomes for patients with diabetes are traditionally classified as being either microvascular or macrovascular in nature. Microvascular outcomes refer to the harmful effects of diabetes on the small blood vessels of the eyes (retinopathy), kidneys (nephropathy), and nerves (neuropathy). Macrovascular outcomes include heart disease and stroke. Studies have consistently demonstrated the impact of glycemic control on microvascular outcomes [3] and a recent 10-year retrospective analysis indicates that early glycemic control may also improve macrovascular outcomes [4]. Irrespective of its effects on microvascular and macrovascular outcomes, glycemic control in patients with diabetes should be complemented by strategies that reduce cardiovascular risk.

For a more comprehensive discussion of diabetes and its association with CVD, readers are referred to the background materials for Operation Diabetes, another national patient care project coordinated by APhA-ASP. For the purpose of Operation Heart, patients with diabetes should be classified as being in the highest risk category for heart disease and should receive education on appropriate risk reduction strategies.

High Sensitivity C-Reactive Protein

As described earlier in these materials, atherosclerosis is a chronic inflammatory process characterized by arterial plaque formation and changes in the vascular endothelium. Many of the traditional risk factors for heart disease are thought to contribute to the atherogenic process in part by increasing the level of systemic inflammation.

Due to the underlying role of inflammation in the atherogenic process, several inflammatory mediators, including high sensitivity C-reactive protein (hs-CRP), have been investigated as potential prognostic markers for the development of CVD. Two meta-analyses demonstrated that elevated concentrations of hs-CRP were associated with an increased risk for major coronary events [5, 6]. Additionally, after adjusting for all other major cardiovascular risk factors, hs-CRP remained an independent predictor of primary cardiovascular events [7].

In a guideline statement addressing the use of hs-CRP in clinical practice, a writing group representing the American Heart Association (AHA) and CDC reviewed the association between hs-CRP and increased cardiovascular risk [7]. Based on their review of the literature, the AHA/CDC writing panel defined specific hs-CRP ranges for which patients are at an increased risk of CVD (summarized in Table 1).
Additionally, their recommendations on the use of hs-CRP in clinical practice include the following:

- As a public health measure, screening of hs-CRP across the entire adult population is not recommended;
- Measuring hs-CRP is a reasonable option for further determining cardiovascular risk in adjunct with other major risk factors for CVD. It is most appropriate in patients with an intermediate level of risk for coronary heart disease (10-year risk 10-20%) to help determine the need for additional cardiovascular risk reduction. Elevated hs-CRP (> 3.0 mg/L) is an indication for intensifying risk reduction strategies, such as more aggressive lifestyle modification or use of pharmacotherapy;
- Measuring hs-CRP in patients at low-risk (10-year risk < 10%) is unlikely to change management and is not currently recommended;
- Patients at high-risk for heart disease (10-year risk > 20%) should be treated with aggressive risk reduction therapies irrespective of hs-CRP concentrations. A measure of hs-CRP may help determine the risk of secondary events in patients with established CVD, but proven secondary prevention strategies should not be withheld based on hs-CRP concentrations; and,
- At this time, serial measurement of hs-CRP should not be used to determine efficacy of therapy.

![Table 1. Risk of Cardiovascular Disease based on hs-CRP [7]](image)

<table>
<thead>
<tr>
<th>hs-CRP level (mg/L)</th>
<th>Risk of Cardiovascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.0</td>
<td>Low</td>
</tr>
<tr>
<td>1.0 – 3.0</td>
<td>Average</td>
</tr>
<tr>
<td>&gt; 3.0</td>
<td>High</td>
</tr>
</tbody>
</table>

High-sensitivity CRP values are included as part of the Reynolds Risk Score calculator, a recently validated tool for determining global cardiovascular risk based on the presence or absence of major risk factors for cardiovascular disease [8, 9]. In both men and women, the Reynolds Risk Score demonstrated better prognostic value than calculations based on data from the Framingham Heart Study (see module on Global Cardiovascular Risk for more information).

**Homocysteine**

Elevated serum homocysteine has been associated with an increased risk for CVD [10], but its pathologic role or potential value as a prognostic risk factor has not been determined. Homocysteine is metabolized by enzymes that require folic acid, vitamin B₆, or vitamin B₁₂ as cofactors. As a result, elevated serum concentrations are most common among individuals with poor dietary intake or inborn errors of metabolism. In patients with normal enzymatic function, increased dietary intake of folic acid, vitamin B₆ and vitamin B₁₂ can reduce homocysteine concentrations to normal levels.

Homocysteine reduction was recently evaluated in a large randomized controlled trial, but it was not associated with a reduction in major cardiovascular events [11]. Although targeting homocysteine concentrations for the purpose of reducing cardiovascular risk is not supported by the literature, patients may benefit in other ways from increased dietary sources of folic acid, vitamin B₆, and vitamin B₁₂. Sources rich in these nutrients include green leafy vegetables and fortified whole grains, both of which are important components of the Dietary Approaches to Stop Hypertension (DASH) diet.

**Psychosocial & Neuropsychiatric Risk Factors**

While few large clinical trials have evaluated the impact of psychosocial and neuropsychiatric factors on cardiovascular risk, some evidence indicates that mood, personality, and social interaction may also influence risk for CVD. Explanations for these effects are reasonable physiologically, as emotion and...
stress can increase concentrations of circulating catecholamines and neurohormones, both of which are implicated in the pathophysiology of many cardiovascular disorders.

In the 1950s, cardiologists Friedman and Rosenman claimed that CVD risk was higher among “Type A” personalities, which they described as individuals who were highly competitive, impatient, and often easily frustrated or hostile. Later investigations confirmed these findings while others have failed to demonstrate a correlation between personality and CVD risk. Some have suggested that specific traits within the Type A personality (e.g., hostility) may increase the risk of developing CVD, but these too are conflicting. In the absence of clear evidence to the contrary, individuals with Type A personalities should not be considered as being at increased risk for CVD based on personality traits alone.

Individuals with Type A personalities must be differentiated from patients with diagnosed medical conditions, such as anxiety disorders or depression. Both of these conditions have been linked to an increased risk for CVD. In several studies, Denollet, et al demonstrate this increased risk among patients with “Type D” personalities, which they describe as being individuals who frequently express negative emotions (e.g., anxiety and depression), and who tend to withdraw from social interaction [12, 13]. Meta-analyses demonstrate that risks of developing CVD increase by as much as twofold in patients with concomitant depression [14]. Finally, depressed patients with established CVD also have poorer outcomes, including a higher risk of death following an acute event [15].
References


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