

Cardiac and Vascular Risk

The Framingham Heart Study has provided the richest source of data on predictors of heart and vascular disease. Much information can be found at the website www.framinghamheartstudy.org/. In 1948, the original cohort of 5,206 adults (two thirds of the adult population of Framingham, MA) were recruited to participate in examinations every 2 years. The offspring study was started in 1971, recruiting 5,124 children of the original participants. In 2001, Generation 3 Study began with 4,095 adult grandchildren of the original participants. Over the decades these people have biennial complete histories, physical exams, and laboratory studies to look for the best predictors of developing coronary artery disease, stroke, atrial fibrillation, and many more cardiac disorders. From 1950 to 2008, various researchers have published 1,973 papers based on Framingham study data. Current emphasis is on biomarkers and genetics as risk factors for heart disease. Several decades ago, the Framingham studies were criticized for underrepresenting minorities, a reflection of the population of the town where recruitment began. Therefore, the Omni study was added in 1994 with 506 new subjects of African-American, Hispanic, Asian, and Native American descent. In 2003, the Omni Second Generation Study recruited an additional 410 minority offspring. Over the years, the Framingham study has provided the best source for identifying risk factors for heart and vascular disease. The studies have resulting in scoring mechanisms for predicting the occurrence of future disease and are now widely used in clinical practice. In recent years the American Heart Association has issued guidelines, based on the current research findings, for evaluating potential risk factors that provide a basis for when population screening should be done. This information guides practice protocols and community education.

CORONARY HEART DISEASE (CHD)

Risk Identification

- ▶ The term “cardiac risk factor” describes the characteristics found in healthy people that are independently related to the subsequent development of CHD. These characteristics are termed modifiable and nonmodifiable.

- ▶ Modifiable cardiac risk factors include hypertension, hypercholesterolemia, low high-density lipoprotein cholesterol (HDL-C) level, diabetes mellitus, tobacco use, and obesity.
- ▶ Nonmodifiable cardiac risk factors include age, gender, and family history of premature CHD in a first-degree relative (males < 55 years, females < 65 years).
- ▶ Patients having experienced a CHD event have the highest risk of experiencing another event. This risk is greater than 20% over 10 years, based on the results of the Framingham studies.

Risk Equivalent

- ▶ Patients with a CHD risk equivalent have the same level of CHD risk (> 20% in 10 years), but have not yet experienced a CHD event.
- ▶ There are 3 CHD risk equivalent groups
 - ▶ Patients with 2 or more cardiac risk factors
 - ▶ Patients with other forms of atherosclerotic vascular disease: peripheral vascular disease, abdominal aortic aneurysm, and symptomatic carotid artery disease
 - ▶ Patients with type 2 diabetes
- ▶ Patients with a 20% or greater 10-year risk of a coronary event should be treated as aggressively as people who already have CHD, regardless of symptom profile.
- ▶ Calculating the CHD risk score is the first part of the approach to lipid management of all adults.
- ▶ Risk calculators can be downloaded from:
 - ▶ <http://tools.cardiosource.org/ASCVD-Risk-Estimator/>
 - ▶ <http://clinicalcalc.com/Cardiology/ASCVD/PooledCohort.aspx>

Core Risk Factors

- ▶ Modifiable
 - ▶ Hypertension
 - ▷ There is a 27% increase in risk for every 7 mm Hg increase in diastolic blood pressure (BP).
 - ▷ Isolated systolic hypertension (systolic BP \geq 160 mm Hg) markedly increases the risk for nonfatal myocardial infarction (MI) and cardiovascular death among general population samples and low-risk groups.
 - ▷ Pulse pressure, a potential surrogate for vascular wall stiffness, predicts first and recurrent myocardial infarction. Higher pulse pressure, especially after age 60, was as strong a predictor of CHD as systolic blood pressure.
 - ▷ With effective antihypertensive therapy, CHD risk is reduced but remains higher than in someone without hypertension. Hypertension treatment is detailed in Chapter 9.
 - ▷ The Joint National Committee (JNC) sets the standards for hypertension treatment. JNC 8 recommendations can be found in Table 7-1 below:

TABLE 7-1
JNC 8 RECOMMENDATIONS FOR HYPERTENSION TREATMENT

Recommendation 1	In the general population aged ≥ 60 years, initiate pharmacologic treatment to lower BP at systolic BP ≥ 150 mmHg or diastolic BP ≥ 90 mm Hg. Treat to goal of SBP < 150 mm Hg and DP < 90 mm Hg. (Grade A)
Recommendation 2	In the general population aged < 60 years, initiate pharmacologic treatment to lower BP at DBP ≥ 90 mm Hg, and treat to goal of DBP < 90 mm Hg. (ages 30–59, Grade A; ages 18–29, Grade E)
Recommendation 3	In the general population aged < 60 years, initiate pharmacologic treatment to lower BP at SBP ≥ 140 mm Hg and treat to a goal SBP of < 140 mm Hg. (Grade E)
Recommendation 4	In the population aged ≥ 18 years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg and treat to goal SBP < 140 mm Hg and goal DBP < 90 mm Hg (Grade E)
Recommendation 5	In the population aged ≥ 18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg and treat to a goal SBP < 140 mm Hg and goal DBP < 90 mm Hg (Grade E)
Recommendation 6	In the general population, including those with diabetes, initial hypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB). (Grade B)
Recommendation 7	In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (For general black population, Grade B; for black patients with diabetes, Grade C.)
Recommendation 8	In the population aged ≥ 18 years with CKD, initial or add-on antihypertensive treatment should include an ACE-I or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Grade B)
Recommendation 9	The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug, or add a second drug from one of the classes in Recommendation 6. The clinician should continue to assess BP and adjust treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an ACE-I and an ARB together in the same patient. If goal BP cannot be reached because of a contraindication, or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy. (Grade E)

Note. Adapted from “2014 Evidenced-Based Guideline for the Management of High Blood Pressure in Adults. Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8),” by P. James, et al., 2014, *JAMA*, 311(5), pp. 507–520.

► **Dyslipidemia**

- ▷ Estimates suggest that 45% of American adults have total cholesterol levels greater than 200 mg/dL and that 20% of American adults have total cholesterol levels of 240 mg/dL or greater.

- ▷ A 10% increase in serum cholesterol is associated with a 20% to 30% increase in risk for CHD.
- ▷ Low-density lipoprotein cholesterol (LDL-C) is the primary target for lipid lowering because of the strength of this independent risk factor for CHD. Non-LDL-C (i.e., HDL and triglycerides) is a secondary target for intervention.
- ▷ The lower the concentration of HDL-C, the greater the risk of CHD.
 - ▷ HDL-C below 40 mg/dL is classified as low.
 - ▷ HDL-C above 60 mg/dL is classified as high and is associated with lower CHD risk.
- ▷ Evidence supports elevated triglyceride (TG) level as an independent predictor of CHD risk.
 - ▷ TG levels in the borderline high and high range (150 mg/dL to 500 mg/dL) are associated with increased CHD risk.
- ▷ Saturated fatty acids increase LDL-C levels. Monounsaturated fatty acids lower LDL-C and do not affect HDL-C.
- ▷ The Adult Treatment Panel 4 (ATP 4) released the following guidelines for treatment of dyslipidemia in 2013:

TABLE 7-2
ATP 4 DYSLIPIDEMIA TREATMENT GUIDELINES

High-Dose Statin	<ul style="list-style-type: none"> • Clinical atherosclerotic disease and age 21-75 (includes MI or angina syndrome, prior arterial revascularization, cerebrovascular accident (CVA) or transient ischemic attack (TIA), peripheral artery disease (PAD; Grade A) • LDL-C \geq 190, age 40-75 (Grade B)
Moderate- or High-Dose Statin	<ul style="list-style-type: none"> • Diabetes, age 40-75 • High dose if 10-yr atherosclerotic cardiovascular disease (ASCVD) risk \geq 7.5% (Grade E) • Moderate dose if 10-yr ASCVD risk $<$ 7.5% (Grade A) • 10-yr ASCVD risk \geq 7.5% and LDL 70-190 (Grade A)
Clinical Judgement	<ul style="list-style-type: none"> • 10-yr ASCVD risk 5%-7.5% and LDL 70-190 (Grade C)

Note. Adapted from ACC/AHA guideline on treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults, by N. Stone et al., 2013, retrieved from https://circ.aha.journals.org/content/early/129/25_suppl_2/s1.full

▶ Diabetes mellitus

- ▷ Type 2 diabetes accounts for about 90% of all diabetes cases. Underlying causes of type 2 diabetes are obesity, physical inactivity, and genetics.
- ▷ Diabetes is associated with an accelerated atheromatous process resulting in increased risk for atherosclerotic disease. This risk qualifies diabetes as a CHD risk equivalent (10-year risk of CHD event \geq 20%).
- ▷ Age-adjusted rates for CHD are two to three times higher among men with diabetes and three to seven times higher among women with diabetes than among their counterparts without diabetes.

- ▷ Three-fourths of all deaths among people with diabetes result from CHD. By age 40, CHD is the leading cause of death in both men and women with diabetes.
 - ▷ There is a twofold increase in mortality in those who have diabetes at the time of MI, as well as increased risk for heart failure.
- ▷ Metabolic syndrome is a constellation of lipid and nonlipid risk factors of metabolic origin. Metabolic syndrome is a generalized disorder closely linked to insulin resistance, implicating impaired insulin action.
 - ▷ Excess body fat (particularly abdominal obesity) and physical inactivity promote the development of insulin resistance.
 - ▷ The diagnosis of metabolic syndrome is made when three or more of the risk determinants are present.
 - Waist circumference (at the iliac crest) greater than 40 inches for men or 35 inches for women
 - Triglyceride above 150 mg/dL
 - HDL-C below 40 mg/dL for men and 50 mg/dL for women
 - BP above 135 mm Hg systolic or 85 mm Hg diastolic.
 - Fasting blood glucose higher than 110 mg/dL
- ▶ Nonmodifiable risk factors include:
 - ▶ Age
 - ▷ 85% of people who die of CHD are age 65 years and older.
 - ▷ About 80% of CHD mortality in people below age 65 occurs during the first MI.
 - ▷ Lifetime risk of developing CHD after age 40 is 49% for men and 32% for women.
 - ▷ In general, men (ages 35–65) have a higher risk for CHD than women. In women, the onset of CHD is generally delayed by 10 to 15 years (ages 45–75).
 - ▶ Gender
 - ▷ The incidence of CHD in women lags behind men by 10 years for total CHD and by 20 years for more serious clinical events such as MI and sudden death.
 - ▷ In men, the three major presentations of CHD (angina, sudden death, and MI) are equally distributed. Women with CHD more frequently present with angina symptoms.
 - ▷ CHD kills more women than all cancers combined.
 - ▷ 50% of men and 63% of women who died suddenly of CHD had no previous symptoms of this disease.
 - ▷ Within one year after their first recognized MI, 25% of men and 38% of women will die.
 - ▷ Within 6 years after a recognized heart attack, 18% of men and 35% of women will have another heart attack.
 - ▷ Women in the United States are more likely to die of CHD than any other cause.
 - ▷ CHD rates in women after menopause are 2 to 3 times those of women before menopause.

- Women taking oral contraceptives who also smoke have an increased risk of CHD.
- ▶ Ethnicity
 - Heart disease is the leading cause of death for people of most ethnicities in the United States, including African Americans, Hispanics, and whites. According to the Centers for Disease Control and Prevention there are disparities in incidence of heart disease based on ethnicity. For American Indians or Alaska Natives, heart disease is second only to cancer.

TABLE 7-3

ETHNIC GROUP	INCIDENCE OF HEART DISEASE
White	5.8%
Black	6.5%
Hispanic	6.1%
Asian/Pacific Islander	3.9%
Native American/Alaskan Native	11.6%

Retrieved from www.cdc.gov/mmwr/preview/mmwrhtml/mm6040a1.htm?s_cid=mm6040a1_w2

- ▶ Family history
 - Family history is considered positive when CHD events are confirmed in first-degree male relatives before age 55 years or first-degree female relatives before age 65 years.
 - Typically, the presence of premature CHD in the family history is accompanied by a family history of other cardiac risk factors.
- ▶ Socioeconomic
 - In developed countries, CHD is a disease concentrated in the lower socioeconomic, less educated sector of the population.
 - In developing countries, CHD is a disease of urban middle and upper classes and is virtually unknown in the traditional country villages.
 - Among the cardiovascular diseases, CHD is the leading cause of death in urban areas in rapidly industrializing countries (e.g., China).

Life Habit Risk Factors (Modifiable)

- ▶ Smoking
 - Smoking is the most important modifiable risk factor for CHD, accounting for 400,000 deaths annually.
 - Compared to nonsmokers, those who consume more than 20 cigarettes per day have a two- to threefold increase in CHD risk.
 - Smoking acts synergistically with oral contraceptives to increase CHD risk.

- ▶ Smoking may enhance oxidation of LDL-C, as well as decrease HDL-C, impair coronary vasodilation, increase C-reactive protein and fibrinogen, and enhance monocyte adhesion to endothelial cells.
- ▶ Smoking increases risk for coronary spasm and for ventricular ectopic activity.
- ▶ Smoking cessation decreases the risk of first MI by 65%.
- ▶ Obesity
 - ▶ Obesity adversely influences other vascular risk factors, causing hypertension, dyslipidemia, glucose intolerance, and insulin resistance.
 - ▶ Obesity is independently associated with left ventricular hypertrophy (LVH), while weight loss can reduce left ventricular mass.
 - ▶ Waist-to-hip ratio, a surrogate for abdominal obesity, is an independent marker of vascular risk for women and older men.
 - ▶ Waist circumference measurements indicating increased risk are greater than 40 inches in men and 35 inches in women.
- ▶ Physical inactivity
 - ▶ Mortality data suggests that more than 200,000 deaths result from inactivity annually.
 - ▶ Physical inactivity is associated with other CHD risk factors including decreased HDL-C, insulin resistance, and hypertension.
 - ▶ Physically fit but overweight people have a CHD risk similar to that of people without CHD risk factors.
- ▶ Diet and nutrition
 - ▶ The effect of diet on risk is mediated through lipids, BP, and obesity.
 - ▶ The Mediterranean diet, which is rich in monounsaturated fats as well as fruits and vegetables, is of growing interest.
- ▶ Alcohol abuse
 - ▶ The relative risk of death from cardiovascular disease (CVD) in moderate drinkers compared to nondrinkers was 0.7 in men and 0.6 in women.
 - ▶ The protective effect of moderate alcohol intake on CVD may be mediated through increased HDL-C, decreased platelet aggregation, and fibrinolysis.
 - ▶ Alcohol abuse leads to hypertension, hemorrhagic stroke, and sudden cardiac death.
- ▶ Mental stress
 - ▶ Mental stress can cause coronary vasoconstriction, particularly in atherosclerotic arteries, reducing myocardial oxygen supply.
 - ▶ Catecholamines promote alterations in thrombosis and coagulation, favoring clot formation.
 - ▶ Increases in coronary deaths during missile attacks and earthquakes have been documented.

Emerging Risk Factors

Although these risk factors have been studied now for more than a decade, the evidence linking them to CVD is stronger for some than for others.

- ▶ **Hyperhomocysteinemia**
 - ▶ Elevated homocysteine levels are independently associated with CVD.
 - ▶ Mechanisms include endothelial toxicity, accelerated oxidation of LDL-C, impaired endothelial-derived relaxation factor, and decreased flow-mediated arterial vasodilation.
 - ▶ Deficiencies in folate and vitamins B₁₂ and B₆ lead to elevated serum levels of homocysteine, while supplementation decreases levels.
- ▶ **Hypercoagulability**
 - ▶ Fibrinogen is positively associated with age, obesity, smoking, diabetes, and LDL-C, and inversely associated with HDL-C, alcohol abuse, physical activity, and exercise level.
 - ▶ The relative risk of cardiovascular (CV) events is 1.8 times higher for people in the top as compared with the bottom third of baseline fibrinogen concentration.
 - ▶ Factor VII levels, plasminogen activator inhibition, and platelet aggregation have been associated with CVD risk.
- ▶ **Estrogen status**
 - ▶ In premenopausal women, the age-adjusted incidence and mortality for CHD is lower than in men; however, the rates converge after menopause.
 - ▶ Aside from lipid benefits (decreased LDL-C with increased HDL-C, apolipoprotein A1 [Apo A1], and triglycerides), estrogen decreases LDL oxidation, promotes endothelial vasodilation, decreases fibrinolytic capacity, and enhances glucose metabolism.
 - ▶ Postmenopausal hormone replacement therapy (HRT) is no longer recommended for cardioprotection. The Women's Health Initiative (WHI), a prospective study, found that hrT increased the incidence of MI, stroke, and blood clots.
- ▶ **Lipoprotein (a) [Lp(a)]**
 - ▶ Studies suggest a positive association between Lp(a) and vascular risk, although levels are elevated after acute ischemia, making measurement unreliable.
 - ▶ Limitations on the utility of Lp(a) screening include lack of testing standardization, variability of levels among racial groups, and unclear predictive value.
 - ▶ LDL reduction markedly reduces any adverse hazard associated with Lp(a).
- ▶ **Triglyceride (TG)**
 - ▶ Elevated levels of TG are related to decreased HDL-C; elevated levels of small, dense LDL particles; and procoagulant state.
 - ▶ Lowering triglyceride results in a significant reduction in CVD events.
- ▶ **Oxidative stress**
 - ▶ Vitamin E, beta carotene, and other natural antioxidants have failed to show a beneficial effect on CHD risk or disease progression.
 - ▶ The American Heart Association (AHA) discourages the use of antioxidant vitamin supplements and recommends dietary modifications.

- ▶ Left ventricular hypertrophy (LVH)
 - ▶ The incidence of LVH increases with age, BP, and obesity.
 - ▶ LVH is independently associated with increased incidence of CVD.
 - ▶ No conclusive data support the theory that a reduction in LV mass can improve CV outcome independent of a decrease in BP.
- ▶ C-Reactive protein (CRP) inflammatory processes
 - ▶ Evidence linking inflammation to atherosclerosis stems from studies focusing on acute and chronic phases of CHD.
 - ▶ Acute-phase reactants such as high-sensitivity C-reactive protein (hs-CRP), ICAM-1 (adhesion molecules), and interleukin 6 (IL-6) and tumor necrosis factor (cytokines) are inflammatory markers measured in the plasma.
 - ▶ hs-CRP and serum amyloid A have been shown in several studies to be markers of risk.
 - ▷ People with elevated hs-CRP levels had a relative risk of future vascular events three to four times higher than people with lower levels, an effect independent of other risk factors.
 - ▷ A recent study found that treating elevated CRP with statins (a known antiinflammatory) in people with normal lipids reduced cardiovascular events.
 - ▷ Routine screening of hs-CRP is not currently recommended by the AHA; however, this may change in the future.
 - ▶ Numerous infectious agents are being considered as possible causes of vascular injury and inflammation (e.g., cytomegalovirus, *Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex virus).
 - ▶ Extravascular foci of chronic infection might include gingiva, the bronchi, the urinary tract (including the prostate), and diverticular disease.

Risk Stratification

As mentioned near the beginning of this chapter, the Framingham Heart Study has developed and updated mathematical health risk appraisal models that relate risk factors to the probability of developing CHD.

- ▶ The new sex-specific models incorporate primary and secondary, or subsequent, risk appraisal.
- ▶ Primary models assess CHD risk in persons free of CV disease, including MI, coronary insufficiency, angina pectoris, stroke, TIA, heart failure, and intermittent claudication.
 - ▶ Risk factors included in the Framingham model are triglyceride level, alcohol use, and menopausal status.
- ▶ Subsequent CHD models are applicable for people with a history of CHD or ischemic stroke who have survived the acute period after the event.
 - ▶ Risk factors include age, blood lipid levels (total cholesterol and HDL-C), diabetes, systolic blood pressure (SBP), and smoking.
- ▶ The probability of developing CHD within a 10-year period is calculated by assigning points to each risk factor. Points are summed and probability of CHD read from a Framingham Risk Table.

- ▶ Example of a 55-year-old male smoker with elevated cholesterol and high blood pressure:
 - ▷ Age: 6 points
 - ▷ Total cholesterol and triglyceride elevation: 10 points
 - ▷ No diabetes: 0 points
 - ▷ Smoker: 4 points
 - ▷ SBP: 140 mm Hg on medication: 4 points
 - ▷ Total points = 24, which indicates a 9% probability of a CHD event within 10 years.
- ▶ Framingham Risk Calculators can be downloaded or used online at:
www.framinghamheartstudy.org/ or <http://hp2010.nhlbihin.net/atpiv/riskcalc.htm>

STROKE

Risk Identification

- ▶ Stroke kills almost 130,000 Americans each year—1 out of every 20 deaths.
- ▶ On average, one American dies from stroke every 4 minutes.
- ▶ Every year, more than 795,000 people in the U.S. have a stroke.
- ▶ About 610,000 of these are first or new strokes.
- ▶ About 185,000 strokes, nearly one in four, are in people who have had a previous stroke.
- ▶ About 87% of all strokes are ischemic, when blood flow is blocked to the brain.
- ▶ About 13% of all strokes are hemorrhagic, caused by bleeding into the brain or into spaces between structures.
- ▶ Stroke costs the U.S. an estimated \$34 billion each year. This includes the cost of healthcare services, medications to treat stroke, and missed days of work.
- ▶ Stroke is a leading cause of serious long-term disability.

Core Risk Factors

▶ Nonmodifiable

The strongest nonmodifiable risk factor is the history of a previous TIA or stroke.

▶ Age

- ▷ The risk of stroke doubles in each successive decade after 55 years of age.
- ▷ 28% of stroke victims are younger than 65 years of age.

▶ Gender

- ▷ Stroke prevalence is higher in men than women, with the exception of those 35 to 44 years old and those older than 85 years, among whom women have slightly greater age-specific incidence than men.

- ▷ Fatality rates are higher in women than men; one in six women who suffer a stroke will die of it.
- ▶ Race and ethnicity
 - ▷ Blacks and some Hispanic Americans have almost double the incidence of stroke in comparison with whites.
 - ▷ The increased incidence of stroke in blacks is because of higher prevalence of hypertension (HTN), obesity (in women), diabetes, increased LP(a) levels, smoking (in men), and low socioeconomic levels.
 - ▷ Black men and women were more likely to die of stroke than white men and women.
 - ▷ Chinese and Japanese men and women have a higher incidence of stroke compared to the general population.
- ▶ Family history
 - ▷ Paternal or maternal history of stroke may be associated with increased stroke risk.
 - ▷ Mechanisms include genetic heritability of stroke risk factors, inheritance of susceptibility to effects of risk factors, and familial sharing of cultural, environmental, and lifestyle factors.
 - ▷ There is a five-fold increase in stroke prevalence among monozygotic (identical) twins in comparison with dizygotic (fraternal) twins.
- ▶ Socioeconomic factors
 - ▷ In one study, women living in economically deprived areas had an increased risk of stroke.
- ▶ Modifiable
 - ▶ Hypertension (HTN)
 - ▷ Major risk factor for both cerebral infarct and intracerebral hemorrhage
 - ▷ The incidence of stroke increases in proportion to both systolic and diastolic BP.
 - ▷ Two-thirds of people who experience a first stroke have BP higher than 160/95 mm Hg.
 - ▷ Isolated systolic hypertension (ISH) is an important risk factor for older adults.
 - ▷ ISH is defined by JNC 8 as systolic BP higher than 160 mm Hg and diastolic BP lower than 90 mm Hg.
 - ▷ The SHEP (Systolic Hypertension in the Elderly Program) trial showed a 36% reduction in incidence of stroke with antihypertensive therapy.
 - ▶ Diabetes, hyperinsulinemia, and insulin resistance
 - ▷ People with insulin-dependent diabetes have an increased susceptibility to atherosclerosis and risk factors (e.g., HTN, obesity, abnormal blood lipids).
 - ▷ Metabolic risk factors known as the metabolic syndrome, which includes hyperinsulinemia and insulin resistance and results in hyperglycemia, increased very low density lipoprotein (VLDL), decreased HDL, and HTN, have been identified in some people with type 2 diabetes.
 - ▷ The relative risk of ischemic stroke in people with diabetes ranges from 1.8 to 8.0.

- ▷ People with glucose intolerance have double the risk of brain infarction compared to those with normal glucose tolerance.
- ▷ Tight control of HTN in people with diabetes significantly reduces stroke incidence.
- ▶ Asymptomatic carotid stenosis
 - ▷ Cerebral ischemic events occurred more frequently in men and among patients with severe (> 75%) carotid artery stenosis, progressing carotid artery stenosis, or heart disease.
 - ▷ The annual risk of stroke was 3.2% over 5 years with 60% to 99% carotid artery stenosis.
 - ▷ Some studies suggest that the rate of stroke may be higher for patients with more severe stenosis and higher for patients with progressing stenosis than for those with stable disease.
 - ▷ As with asymptomatic carotid bruit, asymptomatic carotid artery stenosis is an important indicator of concomitant ischemic cardiac disease.
- ▶ Atrial fibrillation (A fib)
 - ▷ The annual risk of stroke for patients with nonvalvular A fib is 3% to 5%, with the condition being responsible for 50% of thromboembolic strokes.
 - ▷ CHADS2 is a simple mnemonic device to help recall the major stroke risk factors in people who have A fib. The name is made from the first letter of each factor.

TABLE 7-4
CHADS2 MNEMONIC FOR STROKE RISK FACTORS

C	Congestive Heart Failure	Points: 1
H	Hypertension	Points: 1
A	Age \geq 75	Points: 1
D	Diabetes Mellitus	Points: 1
S2	Stroke or TIA	Points: 2
TOTAL POINTS		ANNUAL STROKE RISK
0		1.9%
1		2.8%
2		4.0%
3		5.9%
4		8.5%
5		12.5%
6		18.2%

- ▶ Other cardiac diseases
 - ▷ 20% of ischemic strokes are caused by cardiogenic embolism from other cardiac diseases (e.g., ischemic cardiomyopathy, valvular heart disease, intracardiac congenital defects).
 - ▷ MI
 - ▷ 8% of men and 11% of women will have a stroke within 6 years after MI.
 - ▷ Post-MI development of A fib is a common source of cardiogenic emboli.
 - ▷ Overall occurrence of stroke in acute MI is 0.8%, with 0.6% being ischemic.
 - ▷ Assessment of risk factors for stroke post-MI demonstrated that preexisting factors such as previous stroke, A fib, old age, heart failure, and heart rate greater than 100 bpm were more important than treatment with thrombolysis, which was a risk factor of borderline significance.
- ▶ Cardiac surgical procedures
 - ▷ Perioperative stroke occurs in 1% to 7% of patients having coronary artery bypass grafting.
 - ▷ History of prior neurologic events, advanced age, female gender, diabetes, and A fib accompanied by low cardiac output syndrome were identified as risk factors for early and delayed stroke.
 - ▷ Other factors include the duration of cardiopulmonary bypass and the presence of aortic atherosclerosis and macroemboli.
- ▶ Hyperlipidemia
 - ▷ One study showed a continuous and progressive increase in thromboembolic stroke rates with rising levels of cholesterol.
 - ▷ An inverse relationship exists between HDL-C level and stroke risk. (High HDL-C is associated with lower stroke risk.)
 - ▷ In the 4S trial (Simvastatin Survival Study), the simvastatin-treated group experienced a 51% reduction in ischemic nonembolic stroke.
- ▶ Sleep apnea
 - ▷ Sleep-related breathing disorder appears to be a risk factor for stroke.
 - ▷ Pathogenic mechanisms are decreased cerebral perfusion, increased coagulability, and diurnal HTN.
- ▶ Sickle cell disease (SCD)
 - ▷ The prevalence of stroke by age 20 in patients with SCD is at least 11%.

Life Habit Risk Factors

- ▶ Smoking
 - ▷ Effects of smoking are multifactorial, affecting both systemic vasculature and blood function.
 - ▷ Some effects include increased arterial wall stiffness, increased fibrinogen levels, increased platelet aggregation, decreased HDL, and increased hematocrit.
 - ▷ Smokers have twice the relative risk of cerebral infarct of nonsmokers.

- ▶ The relative risk of stroke among former smokers was 1.34 in the Nurses' Health Study and 1.26 in the Physician's Health Study.
- ▶ Stroke risk declined to the level of nonsmokers at 5 years from cessation.
- ▶ Exposure to environmental tobacco smoke caused a 20% to 70% increased risk of coronary events.
- ▶ **Obesity**
 - ▶ Obesity increases the risk of stroke because of the association with HTN, hyperglycemia, and abnormal blood lipids.
 - ▶ Abdominal obesity in men is an independent risk factor for stroke.
 - ▶ Weight gain in women is an independent risk factor for stroke.
- ▶ **Physical inactivity**
 - ▶ Several studies have demonstrated an inverse association between levels of physical activity and stroke incidence.
 - ▶ Protective effects of physical activity may be mediated through its role in controlling HTN, cardiovascular disease, diabetes, and body weight. Other mechanisms include decreasing fibrinogen and platelet activity and increasing tissue plasminogen activator activity and HDL concentration.
- ▶ **Diet and nutrition**
 - ▶ Data regarding the effects of general nutritional status on stroke are limited.
 - ▶ An increment of one serving of fruit and vegetables per day was associated with a 6% decreased risk of stroke.
- ▶ **Alcohol abuse**
 - ▶ Two drinks per day (one drink = 12 oz beer, 4 oz wine, 1.5 oz 80-proof spirits, or 1 oz 100-proof spirits) have a protective effect against stroke.
 - ▶ Risk for stroke increases for those drinking more than five drinks per day compared to nondrinkers.
 - ▶ There is a direct, dose-dependent effect of alcohol consumption on hemorrhagic stroke.
- ▶ **Drug abuse**
 - ▶ Studies examining the effects of illicit drug abuse on stroke risk have been neutral.
 - ▶ Pathogenesis of stroke in this subset of patients is likely multifactorial (e.g., sudden increases in BP, vasculitis).

Emerging Risk Factors

- ▶ **Hyperhomocysteinemia**
 - ▶ Homocysteine concentrations increase with age, with men having higher levels than women, especially at younger ages.
 - ▶ Homocysteine is toxic to the vascular wall and this may include cerebral arteries.
 - ▶ Case-controlled studies have shown an association between hyperhomocysteinemia and stroke. However, no randomized trials have been done to determine whether lowering levels decreases the risk of stroke.

- ▶ **Hypercoagulability**
 - ▶ Limited data exists on the association between antiphospholipid antibodies and cerebrovascular arterial thrombosis.
 - ▶ In one study, elevated anticardiolipin antibody was demonstrated to be an independent stroke risk factor across three ethnic groups, conferring a fourfold increased risk of ischemic stroke.
 - ▶ Studies examining other coagulation abnormalities (factor V Leiden, protein C deficiency, protein S deficiency, antithrombin III deficiency) have been inconclusive.
- ▶ **Hormone replacement therapy (HRT)**
 - ▶ Postmenopausal hrT appears to increase stroke risk. The WHI and the Framingham Heart Study that found a 2.6-fold increase in the relative risk of atherothrombotic stroke among women receiving hrT compared to nonusers.
- ▶ **Oral contraceptive use**
 - ▶ The risk of ischemic stroke is increased in oral contraceptive users, but the absolute increase in risk is small because of the low stroke incidence in this population. The greatest risk is for stroke among oral contraceptive users is in women over 35 who also smoke.
- ▶ **Lipoprotein (a) [Lp(a)]**
 - ▶ Lp(a) is an independent risk factor for ischemic stroke, especially in young adults.
 - ▶ The ratio of apolipoprotein B to apolipoprotein A1 was associated with carotid atheroma.
- ▶ **Inflammatory processes**
 - ▶ Atherosclerosis, the most common cause of stroke, is now believed to be a disease of chronic inflammation.
 - ▶ *Chlamydia pneumoniae* has been identified in atherosclerotic carotid plaques and localizes to regions of altered plaque morphology.
 - ▷ The relationship between serum antibody titers to *C. pneumoniae* and stroke is likely because of its role in plaque progression and destabilization.
 - ▷ The benefit of antibiotic therapy for *C. pneumoniae* is unclear.
 - ▶ High-sensitivity C-reactive protein (hs-CRP) and serum amyloid A, markers of acute infection, may be associated with stroke.
 - ▷ Levels are elevated in smokers and in healthy men with vascular risk factors.
 - ▷ Plasma hs-CRP levels are significantly and positively associated with risk for stroke.

Risk Stratification

The Framingham Heart Study has developed a health risk appraisal for predicting the risk of stroke.

- ▶ Risk factors measured include age, systolic BP, use of antihypertensive therapy, diabetes, smoking, prior CVD (coronary heart disease, cardiac failure, intermittent claudication), atrial fibrillation, and LVH measured by electrocardiogram.

- ▶ The 10-year probability of stroke is determined according to a point system. Points associated with each risk factor are summed. Risk associated with number of points is determined from a Framingham Stroke Risk Profile.
 - ▶ Example of a 70-year-old male, smoker with hypertension and diabetes:
 - ▷ Male age 70: 5 points
 - ▷ SBP 180 mm Hg: 7 points
 - ▷ On HTN therapy: 2 points
 - ▷ Diabetes: 2 points
 - ▷ Smoker: 3 points
 - ▷ Total = 19 points = 32.9% probability
 - ▷ This patient has a 32.9% 10-year probability of stroke, equating to a stroke risk 2.4 times higher than average.

PERIPHERAL VASCULAR DISEASE

Risk Identification

Peripheral vascular disease (PVD) is a manifestation of the atherosclerotic process that affects 12% to 14% of the general population.

- ▶ Approximately one half of the 8.4 million Americans with PVD are symptomatic.
 - ▶ An estimated 840,000 present with critical leg ischemia.
 - ▶ Approximately 3.4 million present with symptoms of intermittent claudication (IC).
- ▶ The prevalence of symptoms of IC increases with age.
 - ▶ 5% of men and 2.5% of women over age 60 experience symptoms of IC.
 - ▶ Three times as many have an abnormal ankle brachial index.
- ▶ Symptoms of IC are usually stable over a 5- to 10-year period.
 - ▶ 73% have no significant change in symptoms.
 - ▶ 16% experience deterioration in symptoms.
 - ▶ 7% require peripheral vascular bypass surgery.
 - ▶ 4% have a major amputation.

Core Risk Factors

- ▶ Diabetes
 - ▶ People with diabetes are three to four times more likely to develop PVD than those without diabetes.
 - ▶ The atheromatous process in people with diabetes particularly affects smaller, more distal vessels, making options for revascularization more difficult.

- ▶ HTN
 - ▶ Those with HTN are 1.5 to 2.5 times more likely to develop PVD than those without.
 - ▶ HTN is a significant risk factor for atherosclerosis when it coexists with other risk factors such as smoking and diabetes.
- ▶ Hyperlipidemia
 - ▶ Relative risk for developing PVD is 1.1 per 10 mg/dL increase in total cholesterol.
- ▶ Age
 - ▶ The prevalence of PVD in Americans increases with age
 - ▷ 3% ages 40 through 59 (about 2.1 million people).
 - ▷ 8% ages 60 through 69 (about 1.6 million people).
 - ▷ 19% ages 70 and older (4.7 million people).
 - ▶ In men, half of new cases of PVD present in the fifth decade.
 - ▶ In general, disease presentation is later in women. By the seventh decade, prevalence is similar.
- ▶ Ethnicity
 - ▶ Risks of developing PVD seem to be race-neutral and are similar in white, African-American, and Japanese-American people.

Life Habit Risk Factor

- ▶ Tobacco use
 - ▶ Cigarette smoking is the most prominent high-risk behavior in developing PVD.
 - ▶ Smokers are 2.5 to 3 times more likely to have PVD than nonsmokers.

Emerging Risk Factor

- ▶ Hyperhomocysteinemia
 - ▶ Genetic and nutritional factors, such as deficiencies in folate, vitamin B₁₂ and vitamin B₆, are associated with increased levels of homocysteine (> 15 mmol/L). It is suggested that hyperhomocysteinemia is an independent risk factor associated with PVD.
 - ▶ The relative risk of developing PVD in those with hyperhomocysteinemia is 1.7 to 2.6.

Risk Stratification

- ▶ PVD is an independent predictor of increased risk of cardiac death.
 - ▶ Half of patients presenting with PVD have symptoms of CHD or electrocardiographic abnormality.
 - ▶ 90% of those with PVD have abnormalities on coronary angiography.
 - ▶ 40% have duplex evidence of carotid artery disease.
- ▶ All-cause mortality rates are two to three times higher for those with PVD than those without PVD.
- ▶ Over 30% of cardiovascular patients have peripheral arterial occlusive disease.

- ▶ Symptomatic PVD carries at least a 30% risk of death within 5 years and almost 50% within 10 years, due primarily to MI (60%) or stroke (12%).
 - ▶ Asymptomatic patients (ankle brachial index < 0.9) have a two- to fivefold increased risk of fatal or nonfatal cardiovascular events.

OVERALL CARDIAC AND VASCULAR RISK

- ▶ Gender and race or ethnicity differences in risk are known across the various diagnoses. This information is important to educate the public and attempt to reduce or eliminate other factors that may increase risk.
- ▶ Table 7–5 provides an overview of the prevalence of disease by race/ethnicity.

TABLE 7-5
PREVALENCE OF SELECT CARDIOVASCULAR DISORDERS BY RACE AND ETHNICITY

	HEART DISEASE	CORONARY HEART DISEASE	HYPER-TENSION	STROKE
White (not Hispanic)	11.4%	6.1%	22.2%	2.2%
Black (not Hispanic)	10.2%	6.0%	31.7%	3.7%
Hispanic	8.8%	5.7%	20.6%	3.7%
Asian American	6.9%	4.3%	19.5%	2.6%
Native American, Alaska Native	10.5%	5.6%	25.5%	NK
Pacific Islander, Native Hawaiian	NK	NK	28.5%	NK

NK = not known.

Note. Adapted from *Heart Disease and Stroke Statistics—2009 Update*, by the American Heart Association, 2009, Dallas: Author.

SUMMARY

This chapter provided an overview of the various risk factors for coronary heart disease, stroke, and peripheral vascular disease. There are many common factors; atherosclerosis is an equal opportunity offender. The Framingham Heart Study was also explained to provide a framework for understanding the background on the topic as well as understanding the Framingham Risk Score. Nonmodifiable, modifiable, and lifestyle factors were discussed. The next chapter will provide background on risk factor reduction. After that, you will find a specific chapter devoted to hypertension and another chapter for hyperlipidemia.

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INTERNET RESOURCES

American Heart Association: <http://americanheart.org/>

Centers for Disease Control and Prevention: www.cdc.gov/HeartDisease/Facts.htm

Framingham Heart Study www.framinghamheartstudy.org/

National Health and Nutrition Examination Survey (NHANES): www.cdc.gov/nchs/nhanes.htm

National Institutes of Health: www.nlm.nih.gov/