Atherosclerosis: Pathogenesis, Morphology, and Risk Factors
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Key Points
- Despite improvements in treating symptomatic cardiovascular diseases due to atherosclerosis, prevention remains a key approach to stemming the tide of morbidity and mortality.
- Atherosclerosis is a disease with multiple potential etiologies; therefore, prevention must address the overall risk factor profile.
- Lifestyle therapies such as smoking cessation, weight management, and physical activity are cornerstones of prevention.
- Antihypertensive therapy and lipid modification, especially with the statins, have emerged as clinically sound drug approaches to risk reduction.
- Novel risk factors may help improve risk stratification or identify new targets of therapy.

Background and History
Once considered an irreversible, inevitable consequence of aging, atherosclerosis (from the Greek atheroma, meaning “gruel” and sclerosis, meaning “hardening”) is now recognized as a disease that may be prevented or managed with treatment. Improvements in medical care have reduced morbidity and increased survival following an atherosclerotic event, such as unstable angina, cerebrovascular accident, and myocardial infarction (MI). However, the successful management of acute coronary syndromes with angioplasty, thrombolytic therapy, and glycoprotein IIb/IIIa inhibitors does not cure the process of atherosclerosis, and the improved survival has resulted in an increased prevalence of patients who must live with a significant atherosclerotic burden. The complications of atherosclerosis result in sizable health expenditures for the United States. Therefore, prevention remains a critical approach to stemming the disease’s progress.

The decline in age-adjusted morbidity and mortality has increased the presence of vascular disease in patients above the age of 75 years. Epidemiologic studies have analyzed morbidity and mortality in people above the age of 75 years and have determined that approximately 70% of all deaths in this age group are due to cardiovascular disease. Additionally, significant morbidity and mortality due to stroke and congestive heart failure also contribute to the public health burden in the elderly. While the incidence of coronary disease is gradually shifting to an older age group, atherosclerosis remains a major threat to younger individuals. Men younger than 60 years of age have a significant risk for the development of premature vascular disease. Cardiovascular disease can be documented in approximately 30% of men younger than 60 years of age, a rate that is significantly higher than that in age-matched women. In older women, the morbidity and mortality related to cardiovascular disease is similar to men.

Effective management for any condition requires a precise knowledge of the pathophysiology of the disease state, sensitive and specific tests for the presence and severity of the disease, and the availability of therapies with demonstrated efficacy. Atherosclerosis is a syndrome with a variety of underlying predisposing causes, and curative therapy is currently not available. However, advances in medical therapy in the treatment of dyslipidemia and hypertension have significantly altered the clinical course of disease and in some cases have resulted in regression of the atherosclerotic process. Additionally, hygienic measures such as smoking cessation, exercise, and weight loss have also proved effective in modifying the risk for cardiovascular disease. The concept of risk factor identification, stratification, and modification has gained considerable clinical importance over the past decade.
The availability of precise diagnostic tests coupled with the development of modulators of the renin angiotensin system, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors [statins], improved antiplatelet therapy, and other advances has contributed to the decline in vascular disease. This chapter discusses the role of risk factor identification and modification as a means to alter the process of atherosclerosis.

Pathophysiology

The response-to-injury hypothesis, originally proposed by Virchow and von Rokitansky and advanced by Ross, extended the injurious role of inflammation as an initial stage of atherosclerosis. The response-to-injury hypothesis postulates that the initiation and progression of occlusive atherosclerotic coronary and peripheral vascular disease involves a nonspecific and stereotypic response incited by endothelial damage or dysfunction. The response-to-injury hypothesis emphasizes the concept of coronary artery disease (CAD) as a syndrome with a multiplicity of potential underlying etiologies that may alter endothelial function. These etiologies include metabolic abnormalities such as hypertension, obesity, dyslipidemia, or diabetes that result in imbalance in lipid permeability, clotting, fibrinolysis, and vascular tone.

Physical damage to the endothelium may occur because of altered shear forces related to elevated blood pressure, immune-mediated injury, or toxic damage as seen with exposure to tobacco inhalants. In response to these injuries, the endothelium suffers functional abnormalities followed by morphologic changes in the vessel wall that include the deposition of lipids, calcium, and connective tissue.

Endothelial Dysfunction

Dysfunction of the endothelial lining of the vascular system is a preclinical stage of atherosclerosis. The endothelium plays a major role in vascular tone. Nitric oxide is synthesized in the endothelium and is a potent, antiinflammatory vasodilator and antiplatelet agent. Additionally, nitric oxide plays a significant role in reduction of cellular adhesion to the endothelial lining. The endothelium is intimately involved in multiple physiologic functions, including regulation of the movement of lipoproteins across the vessel wall, the balance between thrombosis and fibrinolysis, and as the site of a variety of enzymes involved in the metabolism of triglyceride-rich lipoproteins, in addition to angiotensin-converting enzyme. Platelets bind to the dysfunctional endothelium and smooth muscle cells are activated via platelet-derived growth factors leading to cellular proliferation. The endothelium produces a variety of vasoactive molecules in addition to nitric oxide. The major vasoconstrictors generated by the endothelium are angiotensin II and endothelin. The vasoconstrictors are counterbalanced by nitric oxide, prostacyclin, bradykinin, and other compounds that are either produced directly or act indirectly to alter the tone of the vessel wall. The deleterious effects of the classical CAD risk factors for coronary disease are partially due to their effects on endothelial function. Dyslipidemic patients experience a physiologic shift in endothelial function to a proatherogenic and prothrombotic state characterized by inappropriate vasoconstriction, the elaboration of a variety of adhesion molecules, and an imbalance between fibrinolytic compounds such as tissue plasminogen activator and its naturally occurring inhibitor, plasminogen activator inhibitor [PAI-1]. The endothelial dysfunction associated with dyslipidemia may be reversed by statin therapy.

Inflammation

The premise that chronic inflammation may play a role in coronary disease has recently been popularized, although the concept is not new. Leukocytosis has been correlated with atherosclerosis risk in epidemiologic and experimental studies. Histologic studies of occlusive coronary artery lesions have demonstrated increased infiltration of inflammatory cells such as T lymphocytes and monocytes into the plaque with a concentration within areas associated with plaque rupture. Cytokines are associated with the degree of inflammation and regulate the migration of monocytes into the subendothelial space following binding to the endothelium through the elaboration of monocyte chemoattractant protein 1 [MCP-1]. The preclinical phase of atherosclerosis is characterized by the attachment of inflammatory cells modulated by the production of vascular adhesion molecules, which localize on the endothelium and bind the circulating cellular elements prior to transmigration into the subendothelial space where conversion to the macrophage occurs. These macrophages express a scavenger receptor capable of recognizing, binding, and internalizing a number of lipoprotein subparticles, especially oxidized low-density lipoprotein [LDL]. Macrophages thus act as localized tissue scavengers and interact with growth factors and chemoattractants, such as platelet-derived growth factor and MCP.

The Infection Hypothesis

The role that infection potentially plays in atherosclerosis has been supported by epidemiologic studies and relatively small prospective trials. Helicobacter pylori, cytomegalovirus, and Chlamydia pneumoniae have all been postulated to be associated with increased risk for coronary atherosclerosis. In a post hoc analysis of the Helsinki Heart Study involving 4081 dyslipidemic men, infection by C. pneumoniae was an independent risk factor for the development of CAD. Although other smaller studies have provided evidence of benefit, the bulk of prospective clinical trial data does not support the use of antibiotic therapy in prevention of cardiovascular events in patients with coronary disease [Table 74.1]. However, the possibility that infection may play a role in atherogenesis has not been totally excluded and will require further study.

Smooth Muscle Cell Proliferation

Platelet-derived growth factor-β enhances the proliferation and activation of smooth muscle cells and fibroblasts. Growth factors such as transforming growth factor-β are produced,
and they also interact in a complex manner with a variety of cell lines to change the physicochemical composition of atherosclerotic plaque. Smooth muscle cells that originate in the vascular media migrate to the subendothelial space and transform from the normal contractile phenotype into a synthetic one that produces growth factors that modulate the localization of cellular elements and connective tissue matrix. Smooth muscle cells have autocrine functions that allow the production and local action of a variety of mediators such as platelet-derived growth factor, which stimulates the extensive deposition of extracellular connective tissue matrix and influences the activity of the expression of scavenger receptors that recognize modified LDL.

### Thrombosis

The role of occlusive intracoronary thrombus in the pathogenesis of acute coronary syndromes has been well established by angiographic trials. Platelet dysfunction, abnormalities in classical coagulation factors, and impairment in fibrinolytic balance have all been linked to risk for coronary disease. Elevated circulating levels of homocysteine, which have been associated with coronary risk, are also increased with hypercoagulability. Factors such as the lupus anticoagulant and factor V Leiden that are predominantly associated with venous thromboembolic disease may also play a role in subgroups of individuals with coronary atherosclerosis.

### Platelet Function

Platelet deposition is the first step in the pathogenesis of acute coronary syndromes following fissuring of a vulnerable plaque. Additionally, platelets may adhere to the dysfunctional endothelium or on an eroded atherosclerotic plaque. Platelet dysfunction interacts with a variety of other risk factors including dyslipidemia and diabetes. Elevated LDL increases the risk for platelet activation and plays an interactive role in the tendency for dyslipidemic patients to have increased platelet-mediated clot formation. Dyslipidemia promotes the binding of fibrinogen to platelets induced by adenosine diphosphate in a linear manner. The alteration of normal physiologic endothelial function associated with increased levels of LDL may increase platelet deposition independent of visible atherosclerosis.

Diabetes mellitus may also increase platelet activation and provides a potential therapeutic target. Cyclooxygenase inhibitors [aspirin], inhibitors of adenosine diphosphate [clopidogrel], and statins have all been demonstrated to alter platelet function in patients with diabetes. The mechanism by which statin therapy alters platelet function is complex but may involve, at least partially, increasing the activity of nitric oxide synthase, thus yielding enhanced generation of the powerful vasodilator and antiplatelet compound nitric oxide. Platelet aggregation is also a function of the relative content of lipids in the platelet membrane. Implementation of statin therapy may reduce the cholesterol content of the platelet membrane and decrease the enhanced aggregation potential. Platelet activity markers such as P-selectin are associated with increased platelet aggregation. Statin therapy has been demonstrated to decrease the circulating levels of these markers and contribute to the vasoprotective effects of statins in addition to LDL lowering.

### Fibrinolytic Balance

The endothelium modulates the balance between clot formation and clot breakdown by producing both plasminogen activators and the naturally occurring inhibitors. Balance between procoagulant and fibrinolytic factors may play a significant role in the generation of an occlusive coronary thrombus. Concentrations of PAI-1, lipoprotein [a], and tissue plasminogen activator may be altered by pharmacologic therapy. Impairment in fibrinolysis may be suggested by measuring levels of lipoprotein [a] or PAI-1, a serpin whose major function is to decrease plasminogen activation and thus result in an impaired ability to lyse a clot. The evidence documents elevated levels of PAI-1 in patients with dyslipidemia, hypertension (especially associated with increased levels of angiotensin II), or diabetes, or those who smoke cigarettes, but the role of measuring this antifibrinolytic compound as a risk factor is controversial. The plasma levels of tissue-type plasminogen activator (t-PA) and PAI-1 have been associated as being a significant marker for recurrent MI. Case-control studies have demonstrated that the increased circulating plasma level of the t-PA/PAI-1 complex is a marker for recurrent MI and reflects impaired fibrinolysis. Statin therapy may alter the balance between coagulation and fibrinolysis in a favorable manner, and it may partially explain the beneficial role of statins in acute coronary syndromes.

### Table 74.1. Effects of antiinfective therapies on risk for coronary artery disease (CAD)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>n</th>
<th>Agent versus placebo</th>
<th>RRR (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIZARD</td>
<td>Stable post MI</td>
<td>7747</td>
<td>Azithromycin</td>
<td>7</td>
<td>.23</td>
</tr>
<tr>
<td>AZACS</td>
<td>ACS</td>
<td>1439</td>
<td>Azithromycin</td>
<td>6</td>
<td>.664</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>ACS</td>
<td>4126</td>
<td>Gatifloxacin</td>
<td>5</td>
<td>.41</td>
</tr>
<tr>
<td>ROXIS</td>
<td>ACS</td>
<td>202</td>
<td>Roxithromycin</td>
<td>77</td>
<td>.032</td>
</tr>
<tr>
<td>STAMINA</td>
<td>ACS</td>
<td>325</td>
<td>Amoxicillin or azithromycin, with metronidazole and omeprazole</td>
<td>36</td>
<td>.02</td>
</tr>
</tbody>
</table>

WIZARD, Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders; AZACS, Azithromycin in Acute Coronary Syndrome; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; ROXIS, Randomized Trial of Roxithromycin in Non-Q-Wave Coronary Syndromes; STAMINA, South Thames Trial of Anti-biotics in Myocardial Infarction and Unstable Angina; MI, myocardial infarction; ACS, acute coronary syndrome; RRR, relative-risk reduction.
Clinical Stages of Atherosclerosis and Diagnostic Tests

The stages of atherosclerosis may be classified as preclinical and clinical. The earlier stages of atherosclerosis are represented by exposure to risk factors over decades that disturbs the physiologic balance of the endothelium and produces changes in vascular morphology that are not visible on angiography or detectable by standard imaging techniques. Symptomatic coronary and other cardiovascular disease are clinical manifestations of atherosclerosis.

Endothelial function may be evaluated on clinical grounds using direct or indirect measures, although a clear and primary role for testing in basic risk stratification has not been established. The normal response of direct intracoronary injection of acetylcholine is vasodilatation. However, in patients with extensive cardiac risk factors or documented endothelial dysfunction, a paradoxical vasoconstriction is induced by acetylcholine and is a marker for a significant disturbance of normal endothelial function.

Noninvasive assessment of endothelial function can also be accomplished with the utilization of flow-mediated dilatation. Blood pressure cuff occlusion of the brachial artery with Doppler assessment of the diameter following 5 minutes of forearm ischemia can be used as a surrogate marker for endothelial function. Normal subjects significantly dilate the brachial artery following release of vascular obstruction. The reactive hyperemia results from the increased release of nitric oxide, and brachial artery dilatation can be blocked by the administration of direct inhibitors of nitric oxide synthase. The clinical correlation between noninvasive brachial artery measurements and direct injection of acetylcholine is a surrogate for coronary endothelial dysfunction, although the correlation coefficient is relatively weak. Improvement in the risk factor profile with control of dyslipidemia, hypertension, weight loss, and cessation of the use of tobacco products have all been associated with improvement in endothelial function. While not frequently measured clinically, endothelial dysfunction can be looked upon as the earliest stage of atherosclerosis, and restoration of endothelial function by risk factor modification has been advocated as a therapeutic target.

Quantitative coronary angiography is the traditional technique for measuring the degree of luminal encroachment of atherosclerotic plaque. Improved understanding of two aspects of the dynamics of atherogenesis has elevated questions about contrast angiography’s overall value. First, the phenomenon of compensatory remodeling implies that the vessel expands to accommodate the growing atherosclerotic plaque while preserving the lumen diameter. Second, rupture of mildly stenotic plaques with consequent thrombotic occlusion of the artery accounts for the majority of coronary events. Together, these two observations suggest that traditional angiography may not detect the presence of smaller lesions at the greatest risk for precipitating heart attack.

Other technologies that image the atherosclerotic lesion may help overcome this limitation. B-mode ultrasonography of the carotid intimal-medial thickness, intravascular ultrasound to quantify plaque volume, cardiovascular magnetic resonance imaging, and computed tomography to measure coronary calcium have all shown promise as measures of disease burden. In clinical practice, however, using these approaches to track the progress of antiatherosclerosis treatment remains a premature recommendation.

Stary Classification

Endothelial dysfunction progresses to pathologically identifiable lesions whose structural and chemical contents have been characterized from a histologic standpoint. The Stary classification of human atherosclerotic lesions has been extensively employed to determine the morphology and relevance of the clinical stages of the atherosclerotic plaque [Fig. 74.1].

Type I Lesion

The type I lesion is the first atherosclerotic lesion that can be anatomically identified. Type I lesions are characterized by the infiltration into the intima of lipid-laden macrophages from the circulation. The macrophage density is increased in areas with intimal thickening. The macrophage cellular elements are also increased in density in anatomic areas known to be associated with an increased prevalence of clinical ischemic syndromes and are felt to represent progression-prone lesions.

Type II Lesion

The type II lesion represents a progressive intensification of the pathologic process that was originally demonstrable in the type I lesion. Type II lesions are microscopically visible and may be stained with Sudan dyes, which react with lipid within the vessel to impart a red color to the involved lesion. The type II lesion has an increased density of lipid-laden monocyte-derived macrophage cells, and increased numbers of T lymphocytes and smooth muscle cells. Type I and type II lesions are generally clinically silent because of minimal if any luminal impingement and are not associated with either a reduction of distal blood flow or an increased incidence of ischemic events. Type II lesions may progress to more advanced atherosclerotic involvement, especially in individuals with risk factors such as dyslipidemia, hypertension, diabetes, and tobacco usage. Progression-prone lesions appear to be affected by mechanical and shearing forces that are present at bifurcations and vascular branch points, and lesions in these areas may progress relatively rapidly in a coronary-prone individual.

Type III Lesion

The Type III lesion has been described as the intermediate or preatheromatous stage of atherosclerosis and is characterized pathologically by the accumulation of extracellular lipid deposition, which is termed the lipid core, presumably generated by the confluence of lipid droplets that have been distributed in various areas of the lesion. Type III lesions progress to a more advanced state with the potential for an increased risk for developing an ischemic event.

Type IV Lesion

The type IV lesion is the first definite atheromatous lesion that may be identified pathologically and represents an
advanced histologic stage. The type IV lesion is characterized by the presence of extracellular lipid, including the deposition of cholesterol crystals in the musculoelastic layer of the vessel, which has also been involved by adaptive intimal thickening. The accumulation of lipid in this area weakens the arterial wall as it displaces structural smooth muscle cells, whose presence may yield stability to the involved area because of their ability to synthesize matrix materials. Type IV lesions are frequently associated with thickening of the coronary artery opposite an anatomic bifurcation. Type IV lesions are generally crescent-shaped and may be associated with mild luminal impingement. However, the type IV lesion may not be identifiable by coronary angiography. Mineral deposition may be identified microscopically or by ultrafast computer tomography and is frequently associated with cellular and lipid debris.

**Type V Lesion**

The type V lesion is defined pathologically by the demonstration of collagen deposition and is referred to as a fibroatheroma. Type V lesions are associated with an increased risk for reduced plaque stability and risk for rupture with the potential for generation of an obstructive thrombus. The fate of the mural thrombus is variable and may be progressive or incorporated into the lesion with further diminution of luminal dimensions, but no acute clinical sequelae. The collagen within the type V lesion is demonstrable between the lumen and the lipid core and is felt to replace proteoglycan matrix within the atherosclerotic lesion. The increased collagen is also associated with increased degrees of smooth muscle cell migration and lipid deposition.

**Type VI Lesion**

Coronary atherosclerosis mortality and morbidity is frequently associated with the type VI lesion, which was referred to as the complicated lesion in prior classifications. The type VI lesion is associated with fissuring or disruption of the surface, which may be associated with the intravascular generation of thrombotic components depending on both local and systemic procoagulant activity. Fissures frequently develop at the margins of a lesion, which is characterized by an increased density of macrophages and foam cells. Fissuring may be enhanced by alterations of the physical shearing forces to which the lesion is exposed and reductions in the tensile strength of the plaque itself. Additionally, members of the metalloproteinase enzyme system (collagenase, gelatinase) generated by the macrophage cell line may weaken the plaque. Plaque fissuring may generate a thrombus on the surface of the lesion whose course is further influenced by thrombogenic risk factors such as increased platelet aggregation, high levels of fibrinogen, and lipoprotein (a).

**Type VII Lesion**

The type VII or advanced atherosclerotic lesion is demonstrable frequently in older adults and is largely calcific in nature. Calcium deposits are demonstrable in areas that are associated with remnants of extracellular lipid and dead lymphocytes, smooth muscle cells, and macrophages. The lipid core is minimal to nonexistent and is frequently entirely replaced by calcium. The deposition of calcium may add tensile strength to the vascular deformity.
TYPE VIII LESION

The type VIII lesion is fibrotic and is also associated with minimal to no lipid involvement. The development of the fibrotic lesion is unknown from a pathogenetic standpoint. The absence of lipid implies that it may have been metabolized, reabsorbed, or not been deposited in the area. Fibrotic lesions may also represent organized thrombosis and have the potential to obstruct the lumen of medium-sized arteries.

Current theories of atherogenesis emphasize the potential of atherosclerosis to evolve as a nonspecific response to a number of potentially damaging factors such as hypertension, dyslipidemia, or tobacco use. With multiple potential predisposing factors, impeding the development of CAD must involve a global approach to risk factor management.

Evidence-Based Medicine

Modifiable Risk Factors

Coronary disease is a syndrome that should be managed with global risk assessment and modification. The Framingham risk score quantifies the 10-year risk for the development of CAD

Framingham algorithm omits risk

of other risk factors. An analysis of the data determined that the 10-year coronary risk prediction score accurately predicted short-term risk for men and women. However, the change in risk factor profiles may alter the lifetime risk, and further evaluation is necessary to generate multivariate risk factors that can reliably predict lifetime risk for coronary disease. Patients with genetic conditions such as familial hypercholesterolemia, even though the overall risk factor score may be modest in the short term, have been recommended to receive aggressive therapy because of their long-term risk of developing symptomatic atherosclerosis.

The concept of identifying and treating modifiable risk factors has gained considerable interest as a means to alter the course of CAD. The epidemiologic studies of risk factors and clinical trials that evaluate the effects of their modification are generally performed in developed countries. However, approximately 80% of the global burden of cardiovascular disease now occurs in developing countries. The INTERHEART trial was a case-control study performed in 52 countries to evaluate the role of potentially modifiable risk factors associated with MI. The purpose of the INTERHEART study was to clarify the potential impact of risk factors in various countries and ethnic groups to determine if the population attributable risks were similar to those seen in studies such as the Framingham Heart Study and the Multiple Risk Factor Intervention Trial. The INTERHEART

![Figure 74.2](Image)

FIGURE 74.2. Framingham risk algorithm. Estimate 10-year risk for coronary heart disease (CHD) events by assessing the risk factors and tabulating a point-score. Risk factors have different numerical values based on age and sex. The Framingham algorithm omits risk factors such as family history of early heart disease, diabetes mellitus, obesity, and physical inactivity. These should be taken into consideration when present.
TABLE 74.2. Major risk factors in the Adult Treatment Panel III (ATP III)

<table>
<thead>
<tr>
<th>Increases risk for coronary heart disease (CHD)</th>
<th>Decreases the risk for CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Low HDL cholesterol</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Family history of premature CHD</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>Age</td>
</tr>
<tr>
<td>Family history of premature CHD</td>
<td>Decreases the risk for CHD</td>
</tr>
<tr>
<td>Age</td>
<td>High HDL cholesterol</td>
</tr>
</tbody>
</table>

Hypertension

Elevation of systolic and diastolic blood pressure is a major modifiable risk factor and continues to have a high prevalence in the United States. The National Health and Nutrition Examination Survey (NHANES) for 1999–2000 demonstrated that 28.7% of the United States population, which accounts for 58,000,000 Americans, is hypertensive despite a concerted effort by public agencies to identify and control blood pressure. The most recent hypertension prevalence studies from the NHANES database documented an increase of 3.7% since the last survey, which was completed in 1991. The analysis of the NHANES data also tabulated the degree of hypertension awareness, treatment, and control. While 68% of subjects were aware of the diagnosis of hypertension, only 31% had adequate blood pressure control, which was defined as a level less than 140/90 mm Hg. Hypertension thus remains an underdiagnosed and undertreated risk factor, and guidelines for diagnosis, goals of therapy, management strategies, and other definitions have been modified by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7). The JNC-7 guidelines were refined on the basis that the risk relation between hypertension and cardiovascular disease is continuous, consistent, and independent of other risk factors. The higher the degree of pressure elevation, the greater the risk for MI, congestive heart failure, sudden cardiac death, cerebrovascular disease, and renal disease. Subjects between the ages of 40 and 70 years have been demonstrated to express a relative doubling of cardiovascular risk with each 20 mmHg increment in systolic blood pressure or 10 mmHg increment in diastolic blood pressure. The extensive epidemiologic data linking hypertension to atherosclerosis is supported by a large number of clinical hypertension treatment trials demonstrating a 30% to 40% reduction in the incidence of stroke and a 20% to 25% reduction in acute MI with antihypertensive therapy. Hypertension is a main contributor to systolic dysfunction, and adequate control of blood pressure has been demonstrated to reduce the risk for the development of congestive heart failure by 50%. The achievement of a 12 mmHg decrease in systolic blood pressure for 10 years prevents one death for every 11 hypertensive patients treated. However, in the presence of documented cardiovascular disease or target organ damage, only nine subjects would require this degree of blood pressure reduction to prevent a death. Despite the compelling clinical trial data that clearly demonstrate benefit of blood pressure reduction, the degree of blood pressure lowering, initial agent employed, and induction of metabolic abnormalities remain controversial.

The early epidemiologic trials linking the presence and severity of hypertension with the risk for vascular disease were predominantly performed in the United States and Europe. The INTERHEART study corroborated that the risks of hypertension persists in developing countries and is independent of ethnic factors. The presence of a history of hypertension prior to the acute event resulted in an odds ratio for the development of a MI of 1.91, which accounted for 18% of the population-attributable risk. Hypertension was associated with a greater odds ratio and total population-attributable risk in women when compared with men. However, the fact that hypertensive women were approximately 10 years older than the male subjects may have biased the results.

Low HDL cholesterol ATP III defines a low HDL cholesterol as thus remains an underdiagnosed and undertreated risk factor, was defined as a level less than 140/90 mm Hg. Hypertension tension, only 31% had adequate blood pressure control, which was associated with a greater odds ratio and total population-attributable risk. Other definitions have been modified by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7). The JNC-7 guidelines were refined on the basis that the risk relation between hypertension and cardiovascular disease is continuous, consistent, and independent of other risk factors. The higher the degree of pressure elevation, the greater the risk for MI, congestive heart failure, sudden cardiac death, cerebrovascular disease, and renal disease. Subjects between the ages of 40 and 70 years have been demonstrated to express a relative doubling of cardiovascular risk with each 20 mmHg increment in systolic blood pressure or 10 mmHg increment in diastolic blood pressure. The extensive epidemiologic data linking hypertension to atherosclerosis is supported by a large number of clinical hypertension treatment trials demonstrating a 30% to 40% reduction in the incidence of stroke and a 20% to 25% reduction in acute MI with antihypertensive therapy. Hypertension is a main contributor to systolic dysfunction, and adequate control of blood pressure has been demonstrated to reduce the risk for the development of congestive heart failure by 50%. The achievement of a 12 mmHg decrease in systolic blood pressure for 10 years prevents one death for every 11 hypertensive patients treated. However, in the presence of documented cardiovascular disease or target organ damage, only nine subjects would require this degree of blood pressure reduction to prevent a death. Despite the compelling clinical trial data that clearly demonstrate benefit of blood pressure reduction, the degree of blood pressure lowering, initial agent employed, and induction of metabolic abnormalities remain controversial. The early epidemiologic trials linking the presence and severity of hypertension with the risk for vascular disease were predominantly performed in the United States and Europe. The INTERHEART study corroborated that the risks of hypertension persists in developing countries and is independent of ethnic factors. The presence of a history of hypertension prior to the acute event resulted in an odds ratio for the development of a MI of 1.91, which accounted for 18% of the population-attributable risk. Hypertension was associated with a greater odds ratio and total population-attributable risk in women when compared with men. However, the fact that hypertensive women were approximately 10 years older than the male subjects may have biased the results.
Despite multiple clinical trials, the potential that a J-shaped relation exists between blood pressure lowering and risk remains controversial. The Hypertension Optimization Trial (HOT) prospectively addressed the potential adverse effects of overzealous blood pressure lowering.\textsuperscript{37} The HOT trial analyzed the effect of achievement of a diastolic blood pressure of ≤90 mm Hg, ≤85 mm Hg, or ≤80 mm Hg on cardiovascular events to determine optimal diastolic pressure and the possible presence of a J-shaped event curve where the risk for CAD would increase at lower levels of blood pressure. The HOT trial demonstrated the risk in diabetic patients with the target rate of ≤80 mm Hg was roughly 50% lower relative to the group whose target rate was ≤90 mm Hg, thereby rejecting the likelihood of a J-point phenomenon.

The International Verapamil Trandolapril Study (INVEST) trial demonstrated that a therapy based on both verapamil and trandolapril was clinically as effective as the atenolol/hydrochlorothiazide-based strategy in subjects with CAD and hypertension.\textsuperscript{38} Further analysis of the INVEST database suggested an increase in mortality in diabetic subjects who were in the lowest quintile of achieved diastolic blood pressure, a finding that is compatible with the J-point hypothesis and continued the controversy over optimal blood pressure levels.\textsuperscript{39} However, a meta-analysis of 61 prospective observational studies that analyzed mortality data in 1,000,000 subjects over a 12.7 million person-year observational period documented no J-point relation.\textsuperscript{40} The Framingham database was also evaluated for the potential of a J-shaped curve relating blood pressure to cardiovascular risk. The analysis of the Framingham database suggested that the greatest risk from a low diastolic blood pressure was in subjects with preexisting CAD. The interpretation of the Framingham morbidity data was that an excess of cardiovascular morbidity and mortality at low diastolic blood pressure is apparent only when the systolic blood pressure is elevated, leading to a widened pulse pressure.\textsuperscript{41}

Hypertension remains a major modifiable risk factor and is currently undertreated in the United States. Intervention to decrease morbidity and mortality from vascular disease should maintain a major focus on the identification and management of patients with elevated systolic and diastolic blood pressure.

**Dyslipidemia**

Dyslipidemia is central to the process of atherosclerosis and is a major modifiable risk factor according to a variety of epidemiologic, genetic, pathologic, and controlled clinical trials in the United States.\textsuperscript{42} Cholesterol is distributed across a variety of lipoproteins that have a variable impact on risk.\textsuperscript{43} Of the lipoproteins, LDL and triglyceride-rich very-low-density lipoprotein (VLDL) and its remnants are of major importance to their atherogenic potential (Fig. 74.3). High-density lipoprotein (HDL) is antiatherogenic. Furthermore, the main protein constituents of LDL and HDL, apo B and apo A1, respectively, have garnered interest as potential predictors of risk. The INTERHEART study evaluated the role of potentially modifiable risk factors in a global analysis involving 52 countries. In a quintile analysis of 15,152 subjects with acute MI when stratified for the level of apo B/apo A1 ratios demonstrated a clear and progressive risk association. Subjects in the highest quintile of apo B/apo A1 ratios had a 3.2-fold relative increase in risk for the development of coronary disease and demonstrated that even when individuals with multiple ethnic and genetic backgrounds were exposed to the classical risk factors, a positive relation between dyslipidemia and coronary atherosclerosis persisted.\textsuperscript{44}

The epidemiologic data obtained in large-scale population studies are strengthened by the close correlation between atherosclerotic complications, dyslipidemia, and genetic syndromes that involve both overproduction of LDL and underproduction of HDL. The molecular genetics of these conditions have been elucidated.\textsuperscript{45,46} Familial hypercholesterolemia is the prototype for the consequences of increased circulating levels of LDL due to the reduced number or activity of the LDL receptor.\textsuperscript{47} The heterozygous form of familial hypercholesterolemia is associated with premature atherosclerosis, and men afflicted with this condition generally demonstrate an increased incidence of coronary disease by the fourth decade. Women are initially protected by their sex, but also begin to demonstrate increased risk of vascular complications with a 10-year lag period compared with the male population. Underproduction of HDL (e.g., familial hypoalphalipoproteinemia) is also generally but not always linked to increased cardiovascular risk, and insights into the complex genetic mechanism have been elucidated.\textsuperscript{45–47}

The data supporting modification of dyslipidemia as a means to reduce cardiovascular and total mortality have dramatically advanced following the advent of statin therapy. The original statin trials were reviewed in the previous edition of this text. Recent statin trials have extended the role of modification of dyslipidemia across a broad spectrum of lipid levels and have clearly demonstrated clinical benefits in multiple subgroups that were previously considered to be at low clinical risk. Additionally, a variety of novel imaging studies using intravascular ultrasound have also extended the role of statin therapy and appropriate LDL goals.

The Medical Research Council/British Heart Foundation Heart Protection Study analyzed the role of lipid lowering in 20,536 high-risk individuals who had been underrepresented.
in previous trials.48 The Heart Protection Study recruited significant numbers of diabetics, women, elderly patients, subjects with peripheral vascular disease, and individuals with relatively normal cholesterol levels. The lipid entry criteria required that total cholesterol be in excess of 140 mg/dL, thus ensuring a large number of subjects with cholesterol levels that previously would not have been classified as requiring therapy. Additionally, subjects in the control group were allowed to begin statin therapy at their attending physician’s discretion, resulting in a significant number of individuals initially randomized to placebo subsequently being treated with statin therapy. The results were analyzed on an intent-to-treat basis and demonstrated a 12.9% reduction in all-cause mortality primarily due to a reduction in coronary death rates. The benefits of simvastatin therapy were consistent across a wide variety of subgroups and provided strong support for aggressive lipid lowering therapy. The Heart Protection Study also demonstrated an approximate 25% reduction of cardiovascular mortality rate in each subgroup when the baseline LDL was stratified into tertiles.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction-22 (PROVE IT TIMI-22) trial evaluated 4162 subjects who had been hospitalized for an acute coronary syndrome.49 The role of intensive therapy was analyzed by a direct comparison of 80 mg of atorvastatin per day to 40 mg per day of pravastatin therapy utilizing a primary composite end point of fatal and nonfatal MI, total mortality, documented unstable angina, revascularization, and stroke. The PROVE IT trial evaluated aggressive therapy over a 24-month period and the results implied that the original goal set for secondary prevention by the National Cholesterol Education Program might be overly conservative. The group randomized to pravastatin achieved a LDL level of 95 mg/dL, which was below the recommended 100 mg/dL target for secondary prevention. The aggressive therapy arm with atorvastatin decreased circulating LDL to 62 mg/dL, which was a level previously proposed to have potential adverse side effects. Aggressive therapy with atorvastatin resulted in a 16% reduction in the hazard ratio in favor of aggressive therapy and established clinical benefit at LDL levels that had been considered to be associated with increased total mortality, violent behavior, intracerebral hemorrhage, or the induction of malignancy.

The mechanisms involved with the risk reduction with aggressive lipid therapy were further analyzed in the Reversal of Atherosclerosis with Aggressive Lipid Lowering trial (REVERSAL),50 which analyzed 654 patients with known coronary disease who were randomized to receive 40 mg of pravastatin as standard therapy versus an aggressive regimen that consisted of 80 mg of atorvastatin. The primary end point was the percentage change in atheroma volume. Aggressive therapy significantly altered the intravascular ultrasound-determined atheroma volume and also resulted in a greater reduction in inflammatory markers (C-reactive protein, CRP), implicating the benefits of both aggressive lipid lowering and antiinflammatory activity with statin therapy.

The implications of the Heart Protection, PROVE IT, and REVERSAL studies, as well as those of two others (Table 74.3), resulted in a reassessment of the National Cholesterol Education Program guidelines for lipid lowering.51 The trials confirmed benefit of aggressive lipid lowering in high-risk patients and supported the ATP III goal of an LDL cholesterol level <100 mg/dL. Additionally, the trial results led to a modification of the LDL cholesterol goal in patients deemed to be at significantly increased CAD risk. Moderate-risk patients who have two or more risk factors and a calculated 10-year risk of 10% to 20% were recommended to have an LDL cholesterol goal of <130 mg/dL. However, the recent trial data extend the potential for benefit and an LDL cholesterol level of <100 mg/dL as a therapeutic option in these individuals. Patients with extremely high risk may benefit from achieving an LDL cholesterol goal of <70 mg/dL as a means to reduce risk of an ischemic event (Table 74.4).

The implications of the Heart Protection, PROVE IT, and REVERSAL studies support the above observations.51 These recommendations appear to be further supported by the results of the Treating to New Targets (TNT) trial.52 The TNT study randomly assigned 10,001 patients with clinically evident coronary heart disease (CHD) and LDL cholesterol levels <130 mg/dL to double-blind therapy with either 10 mg/day or 80 mg/day of atorvastatin. Patients were followed for a median of 4.9 years. The mean on-treatment LDL cholesterol levels were 77 mg/dL with 80 mg of atorvastatin and 101 mg/dL with 10 mg of atorvastatin. There was

<table>
<thead>
<tr>
<th>Trial</th>
<th>Baseline LDL cholesterol</th>
<th>On-Tx LDL cholesterol (% reduction)†</th>
<th>Agg. Tx event* rate</th>
<th>Moderate Tx or Placebo event* rate</th>
<th>RRR (%)</th>
<th>ARR (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT</td>
<td>146</td>
<td>UC: 121 (16)</td>
<td>14.9%</td>
<td>15.3%</td>
<td>1</td>
<td>0.4</td>
<td>.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P: 104 (30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCOT</td>
<td>132</td>
<td>90 (32)</td>
<td>1.9%</td>
<td>3.0%</td>
<td>36</td>
<td>1.1</td>
<td>.0005</td>
</tr>
<tr>
<td>HPS</td>
<td>-132</td>
<td>-89 (32)</td>
<td>12.9%</td>
<td>14.7%</td>
<td>13</td>
<td>1.8</td>
<td>.0003</td>
</tr>
<tr>
<td>PROSPER</td>
<td>147</td>
<td>97 (34)</td>
<td>14.1%</td>
<td>16.2%</td>
<td>15</td>
<td>2.1</td>
<td>.014</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>106</td>
<td>P: 95 (22)</td>
<td>22.4%</td>
<td>26.3%</td>
<td>16</td>
<td>3.9</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A: 62 (51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†From baseline.

| Table reports primary end points for studies: ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), all-cause mortality; ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm), nonfatal MI or CHD death in, HPS (Heart Protection Study), all-cause mortality; PROSPER (Prospective Study of Pravastatin in the Elderly at Risk), composite of MI, CHD death, or stroke; PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy), composite of any death, MI, unstable angina, revascularization or stroke.

Table 74.4. Statin trials that influenced ATP III 2004 update
greater incidence of persistent elevations in liver amino-
transf erase levels in the high-dose group, but a 22% relative
risk reduction in recurrent cardiovascular events [ hazard
ratio, 0.78; 95% confidence interval, 0.69 to 0.89; p < .001].
There was no difference between the two treatment groups
in overall mortality. Therefore, TNT affirms the cardiovas-
cular benefit of aggressive therapy to lower LDL cholesterol
in stable CAD patients, with the caution that higher-dose
statin therapy may increase liver enzymes.

TOBACCO USE

The use of tobacco products is a major modifiable risk factor
for the initiation and progression of coronary atherosclerosis.
The rate of tobacco use in adults has declined by over
40% over the past four decades, although 23% of adults in
the United States population still smoke cigarettes.53
Smoking has been estimated to account for 30% of all coro-
nary mortality in the United States, and there is no appar-
ent level below which the intake of cigarette smoke is not
harmful. The epidemiologic data in the United States and
Europe were supported by the INTERHEART study, which
noted a strong and graded relation between the number of
cigarettes smoked and the subsequent risk for MI.54 The
odds ratio increased to the degree that individuals who
consumed more than 36 cigarettes per day had a ninefold
increase in risk compared with nonsmokers, and no plateau
or threshold in the dose response could be documented.
The consumption of as few as five cigarettes per day increased
the risk of CAD, suggesting there is no safe level of tobacco
consumption. However, if cessation of tobacco use is not
possible, the risk of MI associated with smoking may be
decreased by the reduction in the number of cigarettes
smoked. Tobacco is also implicated in a variety of non-
cardiac diseases including cancer, emphysema, peripheral
vascular disease, and other conditions.

The epidemiologic association between the use of tobacco
products and atherosclerosis is compelling. However, the
mechanism of vascular damage is complex and multifactor-
ial. Tobacco smoke consists of a variety of potentially toxic
substances that may play a role in the earlier stages of CAD
in addition to the resultant hypercoagulable stage, which is
associated with the chronic use of tobacco products. Nicot-
ine is a major component of cigarette smoke and stimulates
the presynaptic neuron with the secondary release of neu-
rotransmitters [ e.g., norepinephrine]. Additionally, tobacco
is associated with a procoagulant state that is produced by
increased circulating levels of β-thromboglobulin and fibrin-
ogen.55 The nicotine-mediated release of norepinephrine may
increase the resting heart rate and blood pressure and increase
platelet aggregation while reducing blood flow.55 Nicotine
also may have direct cytotoxic effects on the vascular endo-
thelium and result in the physiologic dysfunction that is
associated with the earliest stage of atherosclerosis. Nicotine
may inhibit cardiac apoptosis, which potentially may play
an additive role in the proliferative cellular aspects of coro-
nary disease.56,57

The inhalation of tobacco smoke also adversely alters
the lipid profile. Tobacco usage significantly lowers HDL
cholesterol.54 The role of smoking and HDL metabolism is
complex and may result from either reduced synthesis or
decreased activity of lipoprotein lipase, a key enzyme in the
catabolism of triglyceride-rich lipoproteins and cholesterol
exchange with HDL.59 The oxidation of LDL is also increased
in users of tobacco products.60 Increased levels of oxidized
LDL stimulate the binding of circulating inflammatory cells
to the endothelium and act synergistically with complement
activation. The use of tobacco products also contributes to
a hypercoagulable state, and the level of fibrinogen is
increased, which has been statistically correlated with ath-
erosclerotic risk.55 Decreased platelet survival and increased
platelet aggregation are demonstrated in the circulation of
smoking cigarettes.61 Additionally, the adverse effects of tobacco
smoke on endothelial function result in an increased level
of thromboxane A2 coupled with a relative subsequent
decrease in prostacyclin, which alters both vascular tone
and platelet function. Cessation of tobacco usage clearly
reduces morbidity and mortality from CAD and should be
actively encouraged in all patients at risk for coronary
atherosclerosis.

DIABETES AND THE METABOLIC SYNDROME

The National Cholesterol Education Program has determined
that diabetes represents a coronary equivalent and should be
aggressively treated even in the absence of documented ath-
erosclerosis. The concept arose from epidemiologic observa-
tions that suggested that the 7-year risk for MI in a diabetic

TABLE 74.4. ATP III treatment decisions based on LDL cholesterol

<table>
<thead>
<tr>
<th>Risk category</th>
<th>LDL cholesterol goal</th>
<th>Initiate TLC</th>
<th>Consider drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD or CHD risk equivalents [10-yr risk &gt;20%]</td>
<td>&lt;100 mg/dL [optional goal: &lt;70 mg/dL]</td>
<td>≥100 mg/dL</td>
<td>≥100 mg/dL [&lt;100 mg/dL: consider drug options]</td>
</tr>
<tr>
<td>Moderately high risk: 2+ risk factors [10-yr risk 10–20%]</td>
<td>&lt;130 mg/dL [optional goal: &lt;100 mg/dL]</td>
<td>≥130 mg/dL</td>
<td>≥130 mg/dL [100–129 mg/dL; consider drug options*]</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors [10-yr risk &lt;10%]</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td>Lower risk: 0–1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL [160–189 mg/dL: drug optional]</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; TLC, therapeutic lifestyle changes; CHD, coronary heart disease.

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL level of <100 mg/dL cannot be achieved by TLC alone. Others prefer use of drugs that primarily modify triglyceride and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

† Almost all people with 0–1 other risk factors have a 10-year risk <10%: thus, 10-year risk assessment in people with 0–1 risk factor is not necessary.
individual without known CAD was equivalent to the mortality rate in nondiabetic individuals who had suffered an MI.64

The age-adjusted prevalence of diabetes is significantly increasing in the United States and is at least partially related to the increasing incidence of obesity. In the period from 1994 to 2002, the diagnosis of diabetes increased by 54% in adults in the United States (4.8 to 7.3%).1 The prevalence of diabetes varies by differing ethnic groups. Non-Hispanic whites have a prevalence of 5.4% compared to Mexican-Americans who have a total prevalence of 8.1%. The precise role of diabetes in risk stratification is complicated in that it frequently coexists with other risk factors, the cluster of which has been termed the metabolic syndrome.64

The prevalence of diagnosed diabetes in the United States is estimated to be 11,100,000 subjects, which accounts for 5.5% of the population. However, the estimated number of individuals who have undiagnosed diabetes is 5,900,000, which is 2.9% of the population, while another estimated 14,500,000 individuals [7.1% of the population] may be prediabetic. The incidence of new-onset type 2 diabetes is 798,000 subjects per year. The increase in the diagnosis of diabetes may be at least partially related to progressive reductions of the level of blood glucose required in diagnostic criteria. However, the increasing prevalence of type 2 diabetes in adolescents is felt to be independent of changes in the diagnostic criteria. The majority of diabetics have type 2 diabetes, but excess risk of cardiovascular disease is seen in both type 1 and type 2 diabetic patients.

The precise role of insulin resistance as an independent mechanism to increase cardiovascular risk is controversial because of the complex interrelation between insulin resistance and other cardiovascular risk factors, as seen in the metabolic syndrome. Insulin resistance is not commonly assessed in large-scale observational studies, and the impact on risk may be underestimated. Meta-analyses have correlated the degree of hyperinsulinemia to adverse cardiac outcomes with up to 11 years of observation.65 Smaller studies utilizing more precise methods for the determination of insulin resistance have also concluded that insulin resistance is an independent risk factor even when controlled for the classical factors [hypertension, dyslipidemia, etc.] known to be associated with atherosclerosis.66

Diabetes is associated with both microvascular [retinopathy, neuropathy] and macrovascular [CAD, cerebrovascular disease] complications. Microvascular disease is clearly correlated with the degree of hyperglycemia and has been demonstrated to be improved by rigorous control of blood sugar. The role of the management of hyperglycemia in the prevention of macrovascular complications is more controversial. Hyperglycemia and the level of hemoglobin A1C have been statistically linked to the risk for CAD in the Framingham study.67 Additionally, a meta-analysis of clinical trials that prospectively evaluated the potential link between hyperglycemia and CAD over a period of 12 years in 95,000 subjects demonstrated a positive correlation between increasing glucose levels and the risk for the development of CAD.68 However, the role and potential clinical benefits attained by strict regulation of circulating glucose levels as a means to decrease risk of macrovascular complications is more controversial.

The Diabetes Control and Complications Trial [DCCT] Research Group randomized 1441 subjects with type 1 diabetes to intensive insulin therapy or usual care and evaluated clinical outcomes.69 The degree of retinopathy, microalbuminuria, and neuropathy was significantly improved with a concomitant increase in the risk for severe hyperglycemia. Macrovascular complications were not improved by intensive therapy of the carbohydrate abnormality in type 1 diabetes. However, the DCCT population averaged 27 years of age and would be expected to have a relatively low risk of atherosclerotic-related complications over the 6.5-year follow-up study. Despite the lack of a statistically significant outcome, a trend for reduction of macrovascular risk was documented in the combined insulin group, which was associated with a relative risk reduction of 41%. Additionally, progression of carotid intimal thickness, which has been validated as a surrogate measurement for the prevalence of atherosclerosis, was improved by intensive management.70

The United Kingdom Prospective Diabetes Study [UKPDS] evaluated 3867 recently diagnosed subjects with type 2 diabetes who were randomly assigned to receive intensive therapy with a variety of oral agents or insulin treatment as compared with conventional therapy.71 The UKPDS trial was conducted over a 10-year follow-up period and the intensive therapy group achieved a hemoglobin A1C of 7%, which was significantly reduced relative to conventional therapy [7.9%]. Despite the improvement in hemoglobin A1C, analysis of the clinical events revealed a statistically nonsignificant relative risk reduction of 16% in the incidence of macrovascular complication rates in the intensive care group, which was accompanied by more frequent episodes of hypoglycemia. Glycemic control as a primary means to reduce the cardiovascular morbidity and mortality associated with diabetes remains controversial; ongoing large, clinical trials will further address this issue.

Dyslipidemia and hypertension should be clearly a major focus of therapeutic interventions in type 2 diabetes because of their high prevalence in this group and the benefit of treatment demonstrated in clinical trials. The Heart Protection Study evaluated 5963 subjects with documented diabetess who were randomized to receive either 40 mg of simvastatin per day or a matching placebo coupled with dietary therapy.72 The administration of simvastatin therapy resulted in a 40 mg/dL LDL differential when compared with the placebo group despite the fact that a significant proportion of the control population was receiving statin therapy by the end of the trial. The composite end point of coronary event stroke, and revascularization fatal and nonfatal MI was analyzed by intention to treat and was associated with a 22% relative risk reduction favoring simvastatin therapy.

The Collaborative Atorvastatin Diabetes Study [CARDS] evaluated 2838 patients with type 2 diabetes without a history of prior MI.73 The subjects enrolled in the CARDS were not markedly hyperlipidemic and the LDL cholesterol levels could not exceed 160 mg/dL [mean of 118 mg/dL at baseline]. The CARDS trial was terminated 24 months prior to the expected duration of the study because of the significant reduction in the primary end point, which was a composite including acute coronary events, coronary revas-
cicularization, or cerebrovascular disease. The prospectively obtained results of the Heart Protection Study and the CARDS strongly support aggressive lipid management in type 2 diabetes even in the absence of prior MI or severe dyslipidemia.78 However, the ALLHAT and high-dose diuretics have long been known to be associated with an increased incidence of diabetes related to chlorthalidone therapy. Noncardioselective beta-blockers and high-dose diuretics have long been known to be associated with the induction of diabetes or abnormal glucose tolerance and adverse lipid effects.76 However, the ALLHAT investigators downplayed the clinical implications of the increased incidence of diabetes related to chlorthalidone therapy because the risk for cardiovascular events was not increased relative to the other cohorts in the 2- to 4-year duration of the ALLHAT, and no difference could be discerned in the morbidity and mortality between the groups. However, the atherosclerotic process related to diabetes is a long-term complication, and thus the impact of drug-induced diabetes may be underestimated in the absence of an extended evaluation period.

In support of the potential adverse clinical effects of drug-induced diabetes is the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) trial, which evaluated the potential cardiovascular complications related to the development of diabetes in subjects treated for hypertension.79 In the study, 375 hypertensive patients were subdivided into the following groups: patients known to be diabetic at the onset of the trial, patients who developed diabetes during the observation period, and patients who remained free of diabetes during the observation period, which ranged up to 15 years. New-onset diabetes occurred in 5.8% of the subjects who initially had normal glucose levels. Predictors for the development of new diabetes included baseline glucose and use of diuretics during the period of observation. The presence of preexisting diabetes was associated with a significant increase in the rate of cardiovascular events compared with nondiabetics, with a hazard ratio of 3.57. Importantly, the development of new-onset diabetes during treatment for hypertension was also associated with a significant increase in cardiovascular risk, with a hazard ratio of 2.92 when compared with individuals who remained free of diabetes during the trial period. The onset of diabetes during therapy for hypertension may have adverse prognostic implications that are not dissimilar from subjects with previously known diabetes.

Subjects with impaired glucose tolerance and abnormal fasting glucose levels who do not fit the strict criteria for diabetes also have an increased risk for atherosclerosis. The ATP III guidelines describe a diagnostic approach for the metabolic syndrome.31 The presence of any three of the risk factors listed may be taken as an indication that the metabolic syndrome is present (Table 74.5). Lifestyle therapy focusing on weight loss is the primary line of intervention for the metabolic syndrome, but a recent joint statement from the American Heart Association, the National Heart, Blood, and Lung Institute, and the American Diabetes Association allows the combination of a statin and a fibrate to treat the atherogenic dyslipidemia often seen in this group.64

<p>| TABLE 74.5. Diagnostic criteria for the metabolic syndrome |
|----------------------------------|----------------------------------|</p>
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference</td>
</tr>
<tr>
<td></td>
<td>Men ≥102 cm (≥40 in.)</td>
</tr>
<tr>
<td></td>
<td>Women ≥88 cm (≥35 in.)</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>Men &lt;40 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Women &lt;50 mg/dL</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein.
Obesity

The incidence and prevalence of obesity in the United States is significantly increasing because of a complex interplay between dietary habits, genetics, and level of physical activity. The World Health Organization has instituted a classification of body mass index cut-off points for the determination of obesity:\textsuperscript{80}

1. Overweight: body mass index of 25 to 29.9 kg/m\(^2\)
2. Class I obesity: body mass index of 30 to 34.9 kg/m\(^2\)
3. Class II obesity: body mass index of 35 to 39.9 kg/m\(^2\)
4. Class III obesity: body mass index of $\geq$40 kg/m\(^2\)

Additionally, the World Health Organization had utilized waist circumference in centimeters as an index of risk. Cardiovascular risk is increased when the waist circumference exceeds 102 cm for men and 89 cm for women. The NHANES demonstrated a progressive increase in the prevalence of subjects who are overweight or fall into the various categories of obesity. The increase in prevalence rates is especially pronounced in diabetics and in truncal obesity, which is progressively increasing in the United States. The First National Health Examination Survey obtained in the time period between 1960 and 1962 was compared with the NHANES data in the years 1999 to 2000.\textsuperscript{81} Obesity was defined as a waist circumference in excess of 40 inches in men and 35 inches in women. Analysis of the NHANES data revealed a significant increase in waist circumference over the time periods in which the NHANES data were obtained. The overall age-adjusted prevalence of abdominal obesity was 12.7\% in the initial NHANES database and is now 38.3\%. Analogous relations were also seen in women, which documented that 19\% of women had abdominal obesity in 1960 compared with 60\% in NHANES-III. The progressive increase in abdominal obesity has had significant public health implications and is related to diabetes, hypertension, and dyslipidemia.\textsuperscript{82} The increase in abdominal obesity has led to a significant increase in undiagnosed diabetes in individuals whose body mass index is $>35$ kg/m\(^2\), and subjects who fulfill these criteria should be screened for the presence of underlying metabolic abnormalities. Despite the continuing efforts in the public health arena to institute measures that would increase physical activity and decrease caloric intake, there is no evidence that the prevalence of obesity in adults and children is decreasing in the United States. However, the role that obesity exerts as a primary independent risk factor remains controversial because of the concomitant association between the components of the metabolic syndrome and a variety of inflammatory and coagulation parameters. However, a significant statistical relation exists between coronary disease and body mass index whether or not the relation is truly independent of associated metabolic conditions.

Increasing body mass index is a powerful predictor of the development of the metabolic syndrome and diabetes. One kilogram increase in body weight will increase the probability of the individual developing diabetes by up to 9\%.\textsuperscript{83} Additionally, increased body mass index and obesity are precursors of the metabolic syndrome and are included in the definition. The distribution of fat in an individual whose weight exceeds the upper limits of normal plays a significant role in the subsequent development of metabolic conditions known to increase CAD. Deposition of fat may be generally classified as abdominal or visceral, and the distribution may be employed as a means to predict the cardiovascular impact of obesity. Visceral fat is associated with the development of the components of the metabolic syndrome including hypertension, diabetes, and dyslipidemia. Visceral fat is deposited within the abdominal cavity and surrounds a variety of internal organs. Visceral fat deposits are characteristic of males and are roughly three times more common in men compared with women. The waist to hip circumference ratio is an easily obtainable measurement that can be correlated with the metabolic complications of obesity.

In addition to predisposing to the incidence of the classic components of the metabolic syndrome, obesity is also associated with a variety of adipokines (tumor necrosis factor-\(\alpha\), interleukin-6, lectin, adiponectin).\textsuperscript{84} Interleukin-6 regulates the hepatic production of CRP, and the presence of the adipokines is compatible with the premise that a significant component of problems related to obesity are inflammatory in nature.\textsuperscript{85}

Hypertension is also commonly associated with increased body mass index. The role of hypertension in obesity at least partially may relate to insulin resistance. Hyperinsulinemia has been associated with increased renal tubular absorption of sodium with subsequent volume expansion, increased sympathetic activity, and vascular remodeling. Thus, hyperinsulinemia at least partially may underlie the hypertension associated with increased body mass index. The presence of insulin resistance and hypertension has a more than additive impact on risk and atherosclerosis in obese subjects. Epidemiologic data demonstrate that prevalence of hypertension may be up to three times higher in type 2 diabetes with obesity and has resulted in more stringent recommendations for blood pressure control. The defining cutoff point for the definition of hypertension in diabetes has now been reduced to 130/70 mm Hg.

Obesity is frequently associated with lipid abnormalities. The most common associated lipid abnormality with obesity is similar to that of type 2 diabetes and has been termed the lipid triad (high triglycerides, low HDL, and the presence of small dense LDL particles). Dyslipidemia in obesity is due to overproduction of VLDL by the liver secondary to increased free fatty acid flux to hepatic tissues and reduced activity of lipoprotein lipase. Thus, overproduction and undermetabolism of triglyceride-rich particles is associated with a significant prevalence of dyslipidemia in the obese subject.

The increased prevalence of obesity in the United States is associated with the aging of the population and has raised concerns over a progressive increase in the cost of medical care due to problems related to obesity, in diabetics, and cardiovascular disease. Epidemiologic projection data adjusted for age, tobacco use, and socioeconomic levels estimate that the average cumulative annual Medicare expenditures would be $76,866 for subjects who were normal weight, compared with $174,752 for severely obese subjects.\textsuperscript{86}

Obesity is a complex metabolic and genetic condition that is widespread in the United States and increasing in prevalence. Obesity is linked to a variety of cardiovascular disorders, and weight loss should be the cornerstone of life-
style therapy in patients at risk for the development of coronary disease.

**Physical Inactivity**

The role of physical inactivity as a primary and independent cardiac risk factor is controversial because of the inherent difficulty in performing prospective controlled trials. However, a vigorous lifestyle has multiple potential health benefits and should be encouraged in the absence of a compelling contraindication. The American Heart Association has recently published guidelines for exercise and physical activity as a means to reduce the risk for vascular disease. A significant problem in epidemiologic studies is related to the definition of terms and precise quantification of oxygen consumption in large population surveys. Physical activity is defined as any bodily movement produced by skeletal muscle that results in caloric expenditure beyond basal metabolic rate. Exercise is a subset of physical activity that is related to a planned program for increasing caloric expenditure and improving ability to perform a physical task. Physical fitness refers to the efficiency of the body at performing activity involved in caloric expenditure and is the sum total of body composition, muscle strength, and other components of the requirements for performing a given set of physical activity. The impact of exercise and physical activity must be quantified as to the amount and intensity of caloric expenditures. The intensity of exercise is defined as a metabolic equivalent where one metabolic equivalent is defined by the basal metabolic rate of 3.5 mm O2/kg/min. The intensity of exercise as the degree of aerobic power is defined as the percent of maximum heart rate or percent of VO2max.

Epidemiologic studies have correlated physical fitness and a high degree of physical activity with reduced risk for CAD. The statistical association is clear, although the possibility exists that subjects who are physically fit because of genetic reasons may have an inherent reduction in overall cardiac risk. Prospective studies have attempted to clarify the causality of relation detected in epidemiologic trials. Increasing physical fitness is associated with a graded reduction in coronary atherosclerosis morbidity and mortality rates. The decrease in rates of coronary atherosclerosis was controlled for other risk factors, but an independent relation between physical activity and decreased coronary risk persisted.

Physical activity may improve physiologic parameters in such ways as reduced weight, and increased HDL cholesterol, myocardial function, and vasodilatory capacity. Therefore, it should be encouraged in individuals as a means to reduce risk by either direct or indirect means. Physical activity is a major determinant of circulating levels of HDL cholesterol. Meta-analysis of 51 studies involving 4700 participants demonstrated an increased level of HDL cholesterol of approximately 5% with exercise training. Additionally, other lipid parameters were also improved with a small but statistically significant decline in LDL cholesterol and triglycerides.

Subjects who are physically inactive have a higher risk for the development of hypertension, and a total of 44 randomized controlled studies have analyzed the effect of physical activity on resting blood pressure. A meta-analysis that included 2674 participants demonstrated that regular exercise achieves a small but statistically significant effect on both systolic and diastolic blood pressure. The effect of exercise on blood pressure was at least partially a function of baseline levels, and individuals whose blood pressure fell into the hypertensive range achieved a greater absolute reduction in systolic and diastolic pressure.

Individuals who are physically inactive frequently demonstrate insulin resistance, the metabolic syndrome, or frank diabetes. Physical activity improves sensitivity to circulating insulin with resultant alteration of glycemic parameters. Type 2 diabetics with elevated hemoglobin A1C levels experienced a reduction in hemoglobin A1C levels of 0.5% to 1% following the institution of exercise training. Additionally, postprandial glycemia and glucose intolerance are also improved by increased physical activity.

Physically inactive subjects tend to be overweight and exhibit increased body mass index. Physical activity, when instituted in combination with a reduction in caloric and fat content of the diet, exerts an additive effect in achieving optimal body weight. The totality of the data with exercise either as an independent variable or acting through other risk factors has led the American College of Sports Medicine to recommend moderate intensity exercise (30 minutes) for most if not all days of the week.

Exercise training is not without risk, and the duration and intensity of exercise in an individual with significant atherosclerotic risk factors should be considered for potential adverse effects. Overly vigorous physical activity has been associated with the induction of malignant ventricular arrhythmias and MI. Thus, previously sedentary adult individuals should undertake a program of physical activity under the guidance of a health professional and with the institution of proper screening methods to avoid cardiovascular complications. The role of screening treadmill stress testing and the consensus conclusion from the American Heart Association considered routine stress testing for the initiation of a vigorous exercise program in healthy men older than 45 years and healthy women older than 55 years to be a class IIb (usefulness and efficacy has not been well established) recommendation.

Physical activity has both direct effects on cardiovascular function and indirect benefit on body weight, blood pressure, dyslipidemia, and glucose control. Individuals at risk for coronary disease should be encouraged to undertake a moderate exercise program as a means to reduce risk for vascular disease.

**Emerging Risk Factors**

Establishing the degree of risk for cardiovascular disease by assessment of the number and severity of risk factors has gained popularity in clinical medicine. However, a significant proportion of patients who suffer a documented acute MI appear to be at low risk based on the commonly accepted risk factors (e.g., hypertension, genetics, dyslipidemia, diabetes, smoking, etc.). This dissonance has led to a search for nontraditional risk factors.

**C-Reactive Protein**

Epidemiologic studies have attempted to correlate the presence and degree of inflammatory markers with the severity
of atherosclerosis. Considerable data have accumulated linking the levels of circulating level of CRP to coronary risk. The prospectively performed Physicians’ Health Study evaluated the relation between CRP and the risk for coronary ischemia and stroke. Men who were clinically free of atherosclerosis with no evidence of a prior MI whose CRP level fell into the highest quartile had a doubling of the relative risk for developing stroke and tripling of the risk for developing an acute MI when compared with subjects in the lowest quartile. The Physicians’ Health Study was controlled for a variety of other risk factors and determined that the increased risk associated with increased levels of CRP was independent when controlled for lipid subfractions, fibrinogen, and smoking habits. Subjects in whom both cholesterol and CRPs were both increased demonstrated a fivefold enhanced risk for future MI. While intriguing, the data from the Physicians’ Health Study did not prove a definite causal relation between increased inflammatory mediators and pathogenesis of atherosclerosis. However, data continue to accumulate that CRP is a significant marker for cardiovascular risk that may be employed in baseline stratification. Whether elevated levels of CRP, myeloperoxidase, fibrinogen, amyloid A, and other markers of inflammation represent an epiphenomenon or a causal factor in atherosclerosis remains to be determined, but increasing evidence supports CRP as being directly involved in the atherosclerotic process.

The role of CRP as it relates to risk for coronary disease has also been evaluated in recent statin trials. Statins have been demonstrated to reduce the level of CRP as a class effect. The decrease in CRP is in support of a potential antiinflammatory effect of these medications. The role of modification of CRP as a clinically relevant pleiotropic effect has been evaluated in recent large-scale lipid trials. The PROVE IT TIMI-22 tested the hypothesis that an aggressive approach to decrease the LDL levels following an acute coronary syndrome would reduce the risk of cardiovascular events. Aggressive therapy (atorvastatin 80 mg) resulted in a 16% reduction in the hazard ratio when compared with moderate care (pravastatin 40 mg). The findings of the PROVE IT trial indicated that the lowering of LDL levels substantially below current target goals for secondary prevention was of clinical value in the reduction of vascular events. The PROVE IT trial also investigated the role of modification of CRP by statin therapy. The reduction in cardiac risk in subjects with LDL levels <70 mg/dL was essentially identical to the risk reduction in subjects who had LDL levels lowered to <100 mg/L. Additionally, the greatest reduction in coronary events was found in subjects who achieved low levels of both LDL and CRP, indicating a potential dual mechanism of benefit for statin therapy.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was a primary prevention trial comparing lovastatin with placebo in 5608 men and 997 women with initial lipid values that were considered to be relatively normal by contemporary standards with the exception of a low HDL. The AFCAPS/TexCAPS was conducted over a 5-year period and resulted in a 37% relative risk reduction for the prevention of a first coronary event. The role of CRP as a basis for targeting statin therapy was also analyzed. C-reactive protein levels were measured at the time of randomization and following 1 year of therapy. The incidence of coronary event rates was significantly correlated with an increased level of CRP at the initiation of therapy. Lovastatin was also demonstrated to decrease the circulating levels of CRP by 15%, which was independent of changes in LDL levels. Lovastatin therapy was associated with a trend towards lower risk in subjects whose total cholesterol to HDL cholesterol ratio was lower than the median level, but who had an elevated CRP, potential suggesting an antiinflammatory mechanism independent of baseline lipids.

A joint statement from the Centers for Disease Control and the American Heart Association has taken a position on the use of inflammatory markers such as CRP in risk assessment. Although the evidence for CRP as a primary determinant of treatment intensity is incomplete, in the context of a patient who appears at the borderline of high risk based on traditional risk factors, the presence of elevated CRP may be considered to justify a more aggressive approach.

**Homocysteine**

Homocystinuria is a rare genetic disease associated with diffuse vascular injury and extensive arterial thrombosis. The role of vascular damage in homocystinuria led to the concept that elevated levels of homocysteine may play a role in the genesis of atherosclerosis. Circulating levels of homocysteine have been correlated with risk for atherosclerosis when controlled for other associated factors and may be considered a novel risk factor. Homocystinuria or marked elevations of circulating levels of homocysteine are uncommon, although modest elevations may occur due to dietary deficiencies of folic acid, hypothyroidism, malignancy, or drugs such as methotrexate. Additionally, homocysteine levels are increased by cigarette smoking. The mechanism by which homocysteine induces vascular damage is complex and multifactorial. Elevated levels of homocysteine are associated with increased oxidative stress, endothelial dysfunction, proliferation of vascular smooth muscle cells, and lipid peroxidation, all of which increase the risk for atherothrombosis. Additionally, in the Framingham Offspring Study homocysteine levels have been correlated with hemostatic risk factors characterized by increased levels of PAI-1, von Willebrand factor, and fibrinogen. Elevated levels of homocysteine are a potentially modifiable risk factor that may be treated by vitamin supplementation with folic acid, vitamin B12, and pyridoxine. However, the Food and Drug Administration has required that all enriched grain products be fortified with folate, which has resulted in a significant reduction in homocysteine levels over the past 10 years and may decrease the role of homocysteine in the pathogenesis of atherosclerosis and decrease the utilization of the measurement of homocysteine as a risk factor.

**Fibrinogen**

Fibrinogen is intimately involved in the clotting process and is a participant in the final step in the coagulation response to vessel injury. The degradation of fibrinogen, which circulates as a glycoprotein, produces soluble fibrin, which is a major component of intravascular clots. Fibrinogen does appear to be a logical risk factor in the atherosclerotic process.
However, fibrinogen is difficult to measure and is altered in a variety of conditions including smoking, infection, diabetes, and hypertension. The role of fibrinogen as a cardiovascular risk factor has been evaluated in 18 prospective studies that involved a total of 4018 subjects with CAD. The comparison of subjects whose fibrinogen levels fell in the upper tertile with the bottom third yields a combined risk ratio of 1.8, which was statistically significant. Fibrinogen has potential impact on cardiovascular risk other than coagulation and is a significant determinant of blood viscosity and promoter of platelet aggregation. However, despite the statistical association between fibrinogen and CAD and a plausible mechanism for the role of this clotting factor in the pathogenesis of disease, prospective clinical trials that selectively reduce fibrinogen as a means to decrease coronary death rates have not been performed.

**Lipoprotein (a)**

Lipoprotein (a) has been proposed to be a risk factor for CAD because of its similarity to LDL and the fibrinolytic proenzyme plasminogen, thus suggesting lipoprotein (a) may be active in dyslipidemia or thrombosis. The homology between apo (a) and plasminogen may provide the mechanism by which lipoprotein (a) would interfere with the conversion of plasminogen to plasmin. However, the role that lipoprotein (a) plays as a risk factor has been conflicting, and clinical trials have resulted in conflicting results. A meta-analysis of prospective studies with at least 1 year of follow-up has analyzed the relation between lipoprotein (a) and CAD. Fatal and nonfatal MI occurred in 5436 subjects in the 27 trials that were eligible for inclusion. Levels of lipoprotein (a) were divided into tertiles in subjects in the upper third were at a 1.6 combined risk ratio when compared with patients in the bottom tertile, which was statistically significant. The data were interpreted to support the role of lipoprotein (a) as an independent risk factor for the development of coronary disease, although further prospective studies would be required to determine the role of lipoprotein (a) in the primary causation of atherosclerosis.

**Tissue Factor**

Tissue factor plays a central role in the initiation of clot formation following vascular injury. Tissue factor binds to factor VII and forms a complex within the extrinsic coagulation pathway by binding to both factor IX and X. Tissue factor expression is a major component in the initiation of intravascular thrombosis in atherosclerosis. Tissue factor levels had been demonstrated to be increased in atheromaous plaque removed from subjects with unstable angina when compared with individuals with ischemic heart disease but a stable pattern. Tissue factor can also be measured in the plasma, and studies have demonstrated that increased levels are present in CAD and diabetes, which potentially allow the use of tissue factor measurements as a risk factor in coronary disease. Tissue factor is potentially modifiable, and a variety of studies have demonstrated that tissue factor is linked to dyslipidemia, and pharmacologic therapy directed at lipid lowering will alter circulating levels. Statin therapy has reduced tissue factor expression in the monocytes in hypercholesterolemic subjects and has also lowered tissue factor antigen. The modification of tissue factor may play a role in the recent demonstration that statin therapy administered acutely in patients with acute coronary syndromes may reduce events. However, the precise role of tissue factor expression in reduction of the initiation or progression of atherosclerosis has not been conclusively demonstrated, although it is a plausible risk factor.

**Stress**

Psychological and emotional stress is difficult to quantitate and thus remains controversial as a major independent cardiac risk factor. However, mental stress has been demonstrated to increase the degree of sympathetic activity, resulting in inappropriate tachycardia and hypertension and potentially increasing risk in an indirect manner. The increase in psychological stress is felt to represent a possible triggering mechanism for acute MI mediated via alteration of plaque vulnerability. The Multicenter Investigation of the Limitation of Infarct Size [MILIS] has implicated the role of emotional upset as a precipitating event for acute MI. The impact of emotional stress following acute MI may be an underlying mechanism for an increased risk of a recurrent event. The effect of emotional stress following an MI has further been evaluated in 460 individuals who were randomized following the acute hospitalization into an usual care group and an experimental group that was monitored for the presence of psychological stress and administered therapeutic interventions to reduce psychological and emotional distress. Individuals who received no special emotional counseling or intervention following the index event had a relative threelfold increase in the risk of a fatal cardiac event over 5 years. Additionally, the subjects also demonstrated a 1.5-fold increase in the risk of recurrent nonfatal MI over the same period. Subjects who entered the 1 year program of identification and interventional therapy did not experience a significant increase in risk, which was compatible with the premise that psychological stress may represent a modifiable cardiac risk factor. Psychological stress has a plausible pathophysiologic mechanism for the induction of cardiovascular ischemia via induction of arrhythmias, hypertension, hypercoagulability, and other pathophysiologic pathways. The role of beta-blockade, antplatelet agents, and intensive psychological intervention will still require large-scale prospective studies prior to clarification.

Emotional stress may be classified into acute and chronic conditions with differing implications for mechanisms and management. Acute psychological stress is defined as the emotional disturbances associated with catastrophic events such as natural disasters or in military exercises. Observational studies have demonstrated a significant increase in civilian MI rates following missile attacks during the Gulf War. Death of a spouse or family member is also associated with sudden cardiac death in subjects who are exposed to this form of stress. A population survey of 95,647 subjects demonstrated a significant increase in risk for acute MI following bereavement for a loved one, which was highest in individuals with preexisting ischemic heart disease. Chronic stress is frequently associated with social and environmental confounders, which are difficult to control in observational studies. Stress is also frequently associated
with social and environmental conditions such as poor nutrition, low income, and difficulty in accessing medical services, which is rarely quantitated. Additionally, hypertension and the use of tobacco products are frequently present as additive factors. The mechanism by which stress could increase coronary risk is multifactorial. Stress-related increase in sympathetic activity could impair the balance between myocardial oxygen supply and demand by increasing heart rate, inotropic state, and afterload. Additionally, coronary vasospasm may also occur with catechol-mediated increases in vascular tone in susceptible individuals. Studies have also demonstrated that the induction of mental stress may impair appropriate vasodilation, as assessed by coronary flow measurements. The failure of the degree of appropriate coronary vasodilation (as opposed to vasospasm) hypothesis has been supported by studies that found a reduction in the predicted increase in coronary flow during episodes of mental stress in vascular regions that are not associated with significant atherosclerotic obstruction. The impaired dilation of the coronaries differs from classic coronary vasospasm, but is characterized by a less than optimal degree of flow increase, which is normally required during periods of increased oxygen needs.

The role of psychosocial stress remains controversial and conflicting results are found. Additionally, the benefits of stress-modifying interventions are also controversial. A meta-analysis of the prospective studies on the relation between stress and CAD suggested that a positive association does exist, although the relative effect is modest. The Approach to the Patient

The ability to identify and modify risk factors associated with CAD has made a major impact on age-adjusted mortality due to atherosclerosis in the United States. The INTERHEART study demonstrated that nine easily measured and potentially modifiable risk factors account for more than 90% of subjects who suffer an acute MI. Dyslipidemia, use of tobacco products, hypertension, diabetes, obesity, psychosocial factors, diet, and physical activity for a significant proportion of the risk associated with MI.

In the clinical setting, the physician should be the leading advocate for risk factor modification. The American Heart Association argues in favor of factors education and prevention beginning in childhood, when risk-enhancing lifestyle influences (poor dietary habits, physical inactivity, tobacco use) are most likely to be initially acquired. Adherence to prevention remains an important obstacle for many patients. The ATP III suggests a number of techniques that may assist the clinician (Table 74.6). Nurses, nurse practitioners, and other members of the medical team can help with appropriate follow-up and reinforcement of prevention recommendations with the patient.

Despite progress in the available treatments and refinement of the understanding of the association between risk factor modification and benefit, CAD remains a leading cause of morbidity and mortality in the United States. Epidemiologic studies and interventional trials demonstrate potential alteration of the clinical risk by addressing the risk factors for CAD. Barring the advent of a unified hypothesis that identifies a single pathologic target for intervention and definitive curative medical therapy for atherosclerosis, the concept of risk factor identification and modification still remains the major focus in the prevention of cardiovascular disease.

Summary

Atherosclerosis was once considered an irreversible and inevitable consequence of aging. Several decades of basic scientific and interventional research have established that aggressive risk factor modification can reduce the risk for—and, in some instances, reverse—atherosclerotic disease. Despite these advances and the proliferation of therapeutic options for treating individual risk factors, continued refinement of risk assessment and further investigation of the interplay of risk factors are needed in order to optimize the identification of at-risk patients and to guide the development of future treatment recommendations. Under ideal conditions, risk factor awareness and management should begin early in life with the promotion of lifestyle, exercise, and diet as the cornerstones of prevention, and should be reinforced throughout adulthood.

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