Chapter 1
Atherosclerosis: Basic Principles and Medical Management
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Learning Objectives

• Understand the pathogenesis of atherosclerosis.
• Describe the progression of atherosclerotic lesions by histologic findings and classification.
• Understand the role of specific cells in atherosclerosis.
• Describe the theories of atherogenesis.
• Understand the various risk factors for atherosclerosis.
• Understand the mechanisms of injury for the main risk factors for atherosclerosis.
• Describe the risk factor modifications that can slow the progression of atherosclerosis.
• Describe the medical management of atherosclerosis.

1. Introduction

Arterial disease is the leading cause of death and significant morbidity in the United States and throughout the world. The American Heart Association estimates that 80 million (36.3%) Americans have cardiovascular disease, leading to 864,500 deaths annually. Patients with peripheral arterial disease (PAD) make up a significant proportion of this group, including 795,000 Americans who will have strokes each year. Stroke itself is the third leading cause of death in the United States with an estimated 143,600 patients dying each year. Those who do survive often have significant neurologic deficits that can become major social and economic burdens to the patients and their families.

Atherosclerosis, or “hardening of the arteries”, is a disease process that leads to plaque formation in the arteries. Over time, these plaques can become hemodynamically significant leading to decreased oxygenation of tissues distal to the disease, or unstable plaques that can rupture and cause thrombosis, embolization, and acute ischemia. Atherosclerosis is a systemic disease that can affect arteries throughout
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the body from the carotid arteries, to the coronary arteries, to the lower extremity arteries. This not only can result in transient ischemic attacks, angina, and claudication, but also can lead to significant morbidity from major strokes, myocardial infarctions (MIs), and extremity gangrene and amputation.

PAD is a significant public health issue requiring extensive long-term care for patients with these serious disabilities, but also because atherosclerosis, and, therefore, PAD is largely preventable or diminishable by avoiding tobacco, fatty foods, and taking medications regularly to control hypertension, diabetes, and hyperlipidemia. Though we now have excellent diagnostic modalities that can help identify patients at risk for atherosclerosis, along with well-planned preventative strategies, patients are often still reluctant to make the necessary lifestyle modifications. It is estimated that for 2009, the total direct and indirect cost of cardiovascular diseases and stroke in the United States was $475.3 billion.

In this chapter, we will discuss the pathogenesis of atherosclerosis, risk factors for development of atherosclerosis the clinical relevance of the disease and discuss preventative modalities and evolving medical treatments.

2. Pathogenesis of Atherosclerosis

2.1 Normal arterial anatomy

In order to understand the process that occurs within the arterial wall that leads to atherosclerosis, one must first begin with the normal anatomy. Arteries are made of three distinct layers that are designed to withstand a lifetime of stress from pulsatile blood flow. These three layers or tunics are the tunica intima, the tunica media, and the tunica adventitia.

The tunica intima, or the endothelium, is the innermost layer of an arterial wall. It consists of a monolayer of endothelial cells with a thick underlying matrix of elastic fibers and collagen. The intimal endothelial cells are responsible for a variety of functions including the regulation of vessel tone and the initiation and formation of thrombus as a response to endothelial injury. The intima receives its blood supply directly by diffusion from the flowing blood within the arterial lumen. An internal elastic membrane, or lamina, separates the intima from the next layer, the media.

The tunica media is the thick middle layer of the arterial wall. It is composed of varying amounts of collagen, elastic fibers, and smooth muscle. The amount of elastin found within the media of an artery decreases progressively from the “elastic” thoracic aorta to the peripheral medium-sized “muscular” arteries, such as the femoral or carotid arteries, to the small high-resistance peripheral vessels. The media provides structure to the vessel and is involved in maintaining vessel tone by responding to signals from the intimal endothelial cells. It is here in the media where
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The atherosclerotic process begins and proliferates. The media receives oxygen and nutrition not only from diffusion of the circulating luminal blood, but also from small vessels (vasa vasorum) that penetrate the outer arterial wall. The media and the adventitia are separated by an external elastic membrane.

The tunica adventitia is the outermost layer of an artery. The adventitia appears fragile and thin; however, its strong collagen and elastic structure make it one of the key components in the overall strength of an artery. The adventitia is composed of collagen, autonomic nerves, and the vasa vasorum that course along and through the adventitia. This layer must be included in a vascular anastomosis in order to prevent future anastomotic breakdown and pseudoaneurysm formation.

2.2 Etiology and progression of disease

The term atherosclerosis comes from the words atheroma and sclerosis. Atheroma is derived from the Greek ather-, means “gruel” or “porridge,” and sclerosis, means “hardening” or “induration.” Arteriosclerosis is a general term that refers to any hardening of the arteries or loss of elasticity, and though the two words are often used interchangeably, technically atherosclerosis is a type of arteriosclerosis. Atherosclerosis describes changes in the arterial wall causing thickening of the vessel wall due to focal accumulation of lipids, fibrous tissue, hemorrhage, and calcium deposits. Atherosclerosis is a complex process that is linked to a combination of factors. These include genetic predisposition (e.g. familial hyperlipidemia and diabetes), mechanical factors (e.g. hypertension and shear stress), environmental factors (e.g. tobacco and fatty food intake), and a robust immune response.

2.2.1 Intimal thickening

Intimal thickening may represent one of the earliest indications of atherosclerotic disease. Intimal thickening is thought to be either an adaptive response, possibly acting to reduce the diameter of the lumen in reaction to chronically reduced blood flow, or a response designed to increase arterial wall thickness secondary to chronically increased wall tensile stress. Focal intimal thickenings have been noted at or near branch points very early in life in the arteries of infants and even in fetuses. However, diffuse fibrocellular intimal thickening can also been seen in a more generalized fashion without clear relation to branches. This results in a diffusely thickened intima that can be even thicker than the media. Lipids do not appear to accumulate in these areas of intimal thickening though they do tend to occur in similar locations as atherosclerotic lesions. Initial work was hopeful that intimal medial thickness, particularly in the carotid artery, would be a simple and useful predictor of atherosclerotic disease, and has been shown to correlate with future cardiovascular risk for stroke.
and MI. However, there are several limitations to measurements of carotid intimal medial thickness (CIMT). The common carotid artery is the vessel generally sampled, whereas atherosclerosis is much more common in the distal internal carotid artery or carotid bulb. There are other contributors to intimal thickening that are not necessarily related to atherosclerosis, including age and hypertension. The measurement of CIMT is highly dependent on the ultrasound equipment, technique, and operator. One of the primary limitations is the inability to distinguish lesions with a necrotic core, which is felt to be a better predictor of atherosclerosis. Future work and improved ultrasound technology may improve results in the area of measuring intimal medial thickness as a predictor of atherosclerotic disease.

2.2.2 Fatty streaks

Atherosclerosis begins in the earliest years of life and tends to affect primarily the large- and medium-sized elastic and muscular arteries. The earliest lesions, the so-called “fatty streaks” are found in young children and even infants. Fatty streaks are yellow and slightly raised lesions often found in the aorta of infants and children. This is a purely inflammatory lesion and is composed of lipid-laden macrophages (foam cells) and T lymphocytes. Cholesterols, specifically low-density lipoproteins (LDL), are the main lipids found in these early lesions, and once oxidized they are engulfed by monocyte-derived macrophages and become foam cells. Stary et al. classified these early lesions into Types I–III (see Classification of Vascular Lesions). Cigarette smoking greatly accelerates the formation of these fatty streaks by increasing the oxidation of LDL and their phagocytosis by macrophages. There is evidence that with exercise, modification of risks factors, and statin medications, these early lesions can stabilize or regress.

2.2.3 Fibrofatty lesions/gelatinous plaques

Another type of early atheroma precursor is the fibrofatty lesion or gelatinous plaque. These lesions were first noted by Virchow in 1856, thought they have been less studied than other lesions. Plasma proteins, particularly the hemostatic components, are thought to be the source of these lesions. These gelatinous plaques are described as translucent and neutral in color, with central gray or opaque areas. They have finely dispersed lipid with collagen strands around the lesions and have a low lipid content and high fluid content. Grossly, they are soft with the gelatinous material separating easily from the arterial wall.

2.2.4 Fibrous plaques

Fibrous plaques appear later in life and are a more permanent lesion. Often found at arterial bifurcations, fibrous plaques are comprised of a lipid core surrounded by
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A capsule made of collagenous and elastic tissue. These lesions are termed Type IV plaques (see Classification of Vascular Lesions), and are composed of large numbers of smooth muscle cells and connective tissue that forms a fibrous cap over an inner yellow core. This soft yellow core contains the highly irritating and inflammatory cholesterol esters and cholesterol oxysterols likely derived from disrupted foam cells. A large number of macrophages are also present. These plaques protrude into the arterial lumen, and in the beginning arterial enlargement compensates for atheroma growth. However, with continued growth, symptomatic stenoses occur along with ulceration, rupture, or overlying thrombosis leading to arterial luminal compromise.

2.2.5 Complicated lesions

Complicated lesions (Types V and VI, see Classification of Vascular Lesions) develop from the fibrous plaque through several potential processes including necrosis, ulceration of the surface of the plaque, calcification, or intraplaque hemorrhage. These are the pathologic developments that lead to the clinical complications of MI, stroke, and gangrene. Ulcerated plaque is thrombogenic and causes platelet aggregation and thrombus formation. Intraplaque hemorrhage can lead to plaque instability and rupture. With the development of a complicated lesion, the elasticity of the arterial wall is lost and the vessel can become narrow leading to stenosis, or degenerate leading to dilation of the arterial wall and aneurysm formation.

2.3 Classification of vascular lesions

In the mid-1990s, Stary and colleagues reported for the American Heart Association Committee on Vascular Lesions. They classified atherosclerotic lesions into six types (Types I–VI). Type I lesions are not visible, but represent the first atherosclerotic changes, including increasing numbers of intimal macrophages and the appearance of foam cells. Type II lesions are the fatty streak lesions, the first grossly visible lesions, which contain layers of macrophage foam cells and lipid droplets within intimal smooth muscle cells (Fig. 1). Types I and II are generally the only lesion types that found in infants and children, although they may also occur later in adulthood. The Type III lesion is the intermediate stage between Type II and Type IV (atheroma, a lesion that can be potentially symptomatic). Type III lesions not only include all the components of Type II lesions, but also contain scattered pools of extracellular lipid droplets and particles that disrupt the coherence of some intimal smooth muscle cells. This extracellular lipid is the precursor to the large, confluent, and more troublesome core of extracellular lipid seen in Type IV lesions (Fig. 2). Beginning around the fourth decade of life, lesions with a lipid core often will have thick layers of fibrous connective tissue or a fibrous cap (Type V lesion). Largely
Fig. 1. Type II and III Lesions. Type II lesions are fatty streaks containing foam cells. The lesion is also comprised of low-density lipoprotein (LDL) particles in the matrix and altered smooth muscle cells. With development of a Type III lesion there are now extracellular aggregates or pools of lipid in the intima and extending into the media. IEL, internal elastic lamina. (From DePalma RG: Atherosclerosis: Pathology, Pathogenesis, and Medical Management. In Moore, WS [ed]: Vascular and Endovascular Surgery: A Comprehensive Review, 7th Edition. Philadelphia, Elsevier Saunders, 2006, p. 93.)

Fig. 2. Type IV Atheroma. With this degree of maturation of the atheroma there is a fibrous cap, central lipid core, macrophage accumulation and zone of active smooth muscle proliferation at the edge of the core. IEL, internal elastic lamina. (From DePalma RG: Atherosclerosis: Pathology, Pathogenesis, and Medical Management. In Moore, WS [ed]: Vascular and Endovascular Surgery: A Comprehensive Review, 7th Edition. Philadelphia, Elsevier Saunders, 2006, p. 92.)
calcified lesions are termed Type Vb, and mainly fibrous lesions with significant connective tissue and little or no lipid or calcium are deemed Type Vc lesions. Once a lesion becomes fissured, develops a hematoma or thrombus, it is deemed a Type VI lesion.

2.4 Atherosclerosis at the cellular level

2.4.1 Endothelium

In early atherosclerosis, including in fatty streaks, endothelial cells in animal and human studies become altered, showing signs of endothelial dysfunction. They begin to be oriented away from the direction of arterial blood flow, show evidence of increased proliferation, become rounded or polyhedral, and increase the formation of multinucleated cells and cilia. This increased cell turnover leads to increased cell death, exposure of subendothelial foam cells, and permeability. As the endothelium becomes more permeable to macromolecules, there is increased mural thrombus formation and tissue factor expression. There is also increased leukocyte adherence with increased expression of VCAM-1 a monocyte adhesion molecule. Increased vasoconstriction of the vessel occurs with decreasing levels of endothelium-derived relaxing factor, nitric oxide, and prostacyclin.

2.4.2 Smooth muscle cells

Experimental models of early atherosclerosis have shown a variety of changes that occur in smooth muscle cells. There is increased expression of dermatan sulfate, stromelysins, proteoglycan, and both Type I and III collagens. Smooth muscles cells are induced to produce a variety of cytokines, such as tumor necrosis factor (TNF), macrophage colony-stimulating factor, and monocyte chemotactant protein-1. These smooth muscle cells ingest and accumulate native and modified lipoproteins by standard receptor pathways and nonspecific phagocytosis. These smooth muscle cells also express increased lipoprotein lipase activity and experimentally display a scavenger receptor like foam cells.

2.4.3 Macrophages

In early atherosclerosis, macrophages proliferate and express a variety of factors that induce further proliferation and uptake of normal and oxidized cholesterols. These include monocyte chemotactant protein-1, macrophage colony-stimulating factor, TNF, intraleukin-1, platelet-derived growth factor, immune antigens, and tissue factor. Plaque macrophages contain increased free and esterified cholesterol and increased acetyl coenzyme A, cholesterol acyltransferase, and acid cholesterol ester hydrolase. These abnormal cells also express the scavenger receptor
15-lipoxygenase and exhibit increased lipoprotein oxidation products in both animal and humans models.

3. Theories of Atherogenesis

3.1 Response to injury hypothesis

There have been several theories of atherogenesis over the decades of study in this area. The most comprehensive and inclusive theory with the most current support is the response to injury hypothesis.

Healthy endothelium provides a smooth and nonadherent surface over which blood can flow. However, this normal endothelial surface can be disrupted or injured by a variety of stressors. Normal healing leads to rapid regeneration of the endothelium. However, if the injury is extensive, the healing response may be accompanied by an influx of inflammatory agents including smooth muscle cells, which causes intimal thickening, or in some sense “scar tissue” formation. According to the response to injury hypotheses, endothelial injury may be caused by a variety of factors including mechanical forces (e.g., hypertension and arterial wall shear stress), circulating metabolites (e.g., oxidized lipids, cigarette smoke), immunologic reactions, and exposure to vasoactive agents. Endothelial injury leads to endothelial dysfunction that results in altered responses to the normal homeostatic properties of the endothelium.

Once the endothelium is desquamated, the subendothelial tissues are exposed leading to T cells, monocytes, and platelets adhering to the injured area in an attempt to repair damaged endothelium. However, in areas of chronic injury, the intimal permeability is altered and there is increased activity leading to an immune-directed inflammatory response involving these monocytes, T cells, and macrophages. All of these, which secrete cytokines, induce cell migration into the medial layer of the vessel. Smooth muscle cells become altered in function increasing the production of extracellular matrix and calcium, and macrophages engulf oxidized lipids and become foam cells. This leads to early atherosclerotic lesions and eventually calcium deposition between vessel layers forming the fibrous cap of atheromas, finally leading to mature plaque formation.

Atheromas not only cause a continued local inflammatory and proliferative response, they can also extend into the arterial lumen causing luminal compromise. The atheroma can then become “unstable” and open or rupture, inducing local thrombosis or releasing thrombogenic debris into the bloodstream and causing embolization.

The local inflammatory response is due to the secretion of cytokines, which leads to a state called “vascular remodeling.” Remodeling is a process where smooth
muscle cell proliferation activates matrix metalloproteinases (MMPs). A few specific
MMPs are able to destroy the structural proteins in the media and adventitia resulting
in a weakened and dilated arterial segment. This dilation initially compensates for
the stenosis, but can also lead to arterial aneurysm formation if unchecked.

3.2 Lipid hypothesis
Lipids have been thought to be an important factor in atherosclerosis since the
time of Virchow. Oxidized lipids are a major component of foam cells, and as
such the lipid hypothesis is a sub-set of the response to injury hypothesis. Patients
with elevated circulating cholesterol have been noted for decades to have a higher
prevalence of atherosclerotic lesions. Patients with familial hypercholesterolemias
provide convincing evidence to support this. These autosomal dominant conditions
have been linked to at least 12 different molecular defects of the LDL receptors.
They occur in approximately 1 in 500 live births. Homozygotes usually die in their
mid-20s due to severe advanced atherosclerosis, and heterozygotes often have total
cholesterol levels ranging up to 350 mg/dL and have severe atherosclerotic disease
as they age.

3.3 Thrombogenic hypothesis
This theory hypothesizes that degenerated blood proteins deposit fibrinous sub-
stances on the intimal arterial surface. These deposits in turn could become athero-
matous masses comprised of cholesterol crystals and goblets. This may also be the
process by which gelatinous plaques are formed.

3.4 Mesenchymal hypothesis
The mesenchymal hypothesis of atherosclerosis explores why physical factors such
as vasoactive agents, shear stress, and repetitive injuries induce a similar sequence
of events in the vessel wall that appears to lead to atherosclerosis. Hauss et al.
postulated that smooth muscle cells migrate from the media to the intima, where
they proliferate and produce connective tissue. Furthermore, they felt that this is a
nonspecific arterial reaction to any injury and that atherosclerosis reflects a normal
arterial response.

3.5 Monoclonal hypothesis
Benditt and Benditt noted that in atherosclerotic lesions, smooth muscle cells are
derived from one or a few smooth muscle cells and, like tumor cells, proliferate in
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an unchecked fashion. This is based on the finding of only one allele for glucose-6-phosphate dehydrogenase in lesions from heterozygotes. In addition, in other studies, it has been noted that the presence of transforming growth factor-beta receptors in human atherosclerosis provides evidence of an acquired resistance to apoptosis, which can also lead to unchecked cellular proliferation.

4. Lesion Arrest and Regression — Plaque Modification

The potential for lesion arrest and regression is crucial to treatment options for patients with atherosclerotic disease. Regression of these lesions, because of a low cholesterol state, has been seen in autopsy studies of starved humans circa World War I. Similar results have been seen in animal models and in human trials of smoking cessation and lipid reduction. The exact mechanism of lesion regression is not completely understood, but this occurs with a clear decrease in the volume of the intimal plaque. It is thought to be related to an efflux or resorption of lipids or extracellular matrix, cell death, and cell migration out of the plaque. Evidence of regression in rhesus monkeys has been shown in studies of serial observations of decreased plaque bulk, decreased luminal encroachment on sequential angiography, decreased plaque lipid, and altered fibrous protein content measured histologically and chemically. Many of these findings were also confirmed on autopsy or surgical observation and biopsy. With lengthy and extensive reduction in blood cholesterol for 42 months in rhesus monkeys, microscopic evidence of regression included the disappearance of macrophages, foam cells, lymphocytes, and extracellular lipids. However, there was no change in the arterial wall calcium deposits. This finding is not surprising and points to calcification as a significantly limiting factor in atherosclerotic lesions. In some cases, fibrous protein increases during regression and may also limit regression; however, this process converts a soft plaque to a fibrous, more stable, and less thrombogenic lesion. Lipid levels must be aggressively reduced in order to induce regression of atherosclerotic plaques.

5. Mechanism of Injury

5.1 Tobacco

Cigarette smoking is an extremely strong inducer of atherosclerosis even in the setting of normal circulating lipids. It is directly related to high mortality from ischemic heart disease, failure of aortic and femoropopliteal bypasses, and limb amputation. The exact mechanisms by which cigarette smoking contributes to atherosclerosis
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and graft thrombosis are not fully understood. However, it is known that cigarette smoke is a powerful oxidizing agent that leads to lipid oxidation, vessel spasm, and vasoconstriction. The main component of cigarette smoke is nicotine, which is a strong pro-inflammatory agent, significantly contributes to endothelial dysfunction by initiating the adhesion cascade and stimulating inflammatory events to induce atherosclerosis and hypertension. Carbon monoxide predisposes to arterial wall injury, producing increased endothelial permeability and influx of LDL and other proteins. Cigarette smoking also causes increased platelet reactivity and lowered HDL levels.

5.2 Hypertension

Prospective studies have shown that premature atherosclerotic disease is independently associated with hypertension. In experimental animals, hyperlipidemia-associated atherosclerosis is accelerated by chronic hypertension. Patients with hypertension often have elevated levels of angiotensin II, the main product of the renin-angiotensin system. Angiotensin II is a potent vasoconstrictor and also stimulates the growth of smooth muscle and increases intracellular calcium concentrations and smooth muscle hypertrophy. Angiotensin II also can increase inflammation and oxidation of LDL by smooth muscle lipoxygenase activity. Hypertension itself also has proinflammatory actions increasing the formation of plasma hydrogen peroxide and other free radicals such as superoxide anion and hydroxyl radicals. These free radicals reduce endothelial formation of nitric oxide, increase leukocyte adhesion, and increase peripheral resistance.

5.3 Shear forces

Advanced atherosclerotic plaques commonly occur at arterial branch points. This finding suggests that local shear stress related to turbulent flow at these branch points may also act as an atherosclerotic accelerating factor. Experimental and clinical observations also have noted that early endothelial injury is more likely to occur in areas of blood flow separation and low shear stress. This is seen clearly in models of the carotid artery bulb (Fig. 3). The layer of blood flowing along the intima is termed the boundary layer. Flow in the middle of the arterial lumen is laminar; however, the outer area of boundary layer separation has slower more disturbed currents. These are areas of low shear force (<4 dyne/cm²) tend to occur at the outer walls of arterial branch points and have been shown to induce endothelial dysfunction.
Fig. 3. Carotid artery bifurcation depicting an area of flow separation near the outer wall of the carotid bulb. High shear stress occurs in areas of rapid flow such as along the inner wall of the carotid bulb. Atherosclerotic lesions usually are located along the outer wall where there is slower flow and lower shear stress produced by the boundary layer separation. (From Zarins CK, Xu C, Glagov S: Artery Wall Pathology in Atherosclerosis. In Rutherford, RB [ed]: Vascular Surgery, 6th Edition. Philadelphia, Elsevier Saunders, 2005, p. 133.)

5.4 Hyperlipidemia

As has been previously discussed in detail in this chapter, elevated circulating lipids play a critical role in atherosclerosis. Patients with elevated circulating cholesterol have significantly higher risk of atherosclerotic lesions. Oxidized lipids are a major component of lipid-laden macrophages or foam cells, which are one of the main contributors to atherosclerotic plaque formation. Modified LDL itself is a chemo-tactic factor for other monocytes and propagates the inflammatory process within the plaque.

5.5 Diabetes

Diabetes is one of the most important and well-documented risk factors for atherosclerosis. Anatomically, diabetes is most often associated with severe tibial and coronary atherosclerosis. Enhanced atherogenesis in diabetes is likely due to abnormalities in apoproteins and lipoprotein particle distribution, particularly elevated levels of lipoprotein (a), which itself is an independent risk factor for
Atherosclerosis. Poorly controlled serum glucose leads to a procoagulant state with in vitro models showing accelerated platelet aggregation. Growth factors, hormones, smooth muscle cell proliferation, and increased foam cell formation are also thought to be further altered in diabetes mellitus leading to accelerated atherogenesis. Hyperinsulinemia and insulin resistance are associated with atherosclerosis, and both insulin and glucose stimulate smooth muscle cell proliferation in the infra-geniculate location in diabetics.

5.6 Infection

Several viruses and bacteria have been shown to be associated (at some level) with atherosclerosis. These include Chlamydia pneumoniae, cytomegalovirus (CMV), Helicobacter pylori, herpesvirus, Porphyromonas gingivalis, and Actinobacillus actinomycetemcomitans. C. pneumoniae or its DNA has been intermittently found in atherosclerotic plaques. It is hypothesized that C. pneumoniae-infected macrophages enter the arterial intima and mediate inflammatory and autoimmune responses via chlamydial heat shock protein 60. Evidence of CMV in atherosclerotic plaques has been noted histologically and in culture. It has been noted that patients who are seropositive for CMV have a high incidence of restenosis after coronary atherectomy.

Periodontal disease has been shown epidemiologically to be related to atherosclerosis. It is thought that periodontal disease might increase circulating cytokine levels, promote a proatherogenic endothelium, and lead to endothelial dysfunction causing a prothrombotic state, cell proliferation, and vasoconstriction. A recent prospective study suggests that the exposure to periodontal pathogens or endotoxin induces systemic inflammation leading to increased risk for cardiovascular disease. The periodontal pathogens Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans have been associated with coronary artery disease and P. gingivalis has been shown to increase IL-6 levels and accelerate atherosclerosis. Results of antibiotic trials as potential treatment for atherosclerotic lesions have been mixed. In a recent pilot study, long-term clarithromycin was noted to reduce recurrent cardiovascular events in subjects without periodontitis, but not in subjects with periodontitis. It was suggested that “periodontitis may overpower the beneficial effects of antibiotics.”

6. Atherosclerosis Basic Principles and Medical Management

6.1 Risk factors for atherosclerotic disease and modification strategies

Many theories and causes of atherogenesis have been postulated and studied, and have lead to a handful of clear risk factors for atherosclerosis. These risk factors have
long been recognized as the framework for a preventative strategy for cardiovascular diseases. The identification of specific cardiovascular risk factors that led to the concept of risk factor modification arose from the findings of the Framingham Heart Study of the 1960s. A risk factor can be simply defined as an entity that can be identified early in the disease course of an individual or group and confers an increased risk of disease development. An essential part of disease prevention in the context of identification of risk factors is the ability for modification of that specific risk factor, usually in the form of behavioral or pharmacologic manipulation.

Cardiovascular disease is increasingly recognized as the largest growing burden of disease for healthcare systems. Though progress in treatment regimens and surgical outcomes once atherosclerotic disease is established has improved morbidity and mortality from cardiovascular complications, there has been a shift in emphasis toward the development of effective clinical guidelines for prevention and modification at an earlier stage in the disease process. Table 1 lists the most common risk factors for atherosclerotic cardiovascular disease.

### 6.2 Smoking

Smoking is the greatest contributor to atherosclerotic cardiovascular disease and the number one cause of preventable deaths in the United States per year. There has been an increase in the number of smokers, despite extensive anti-smoking campaigns, and smoke-related deaths continue to rise particularly in the developing world.

A dose-related phenomenon has been described for cigarette-smoking that correlates with increased rates of coronary events, ischemic strokes, and peripheral vascular disorders. Despite this dose-effect, complete smoking cessation has been
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demonstrated to be the only significantly effective approach to reduce health-risks associated with smoking. Smoking cessation remains a pivotal part of cardiovascular disease prevention. However, initiatives aimed at improving public awareness of the deleterious effects of ischemic heart disease, peripheral vascular disease including amputation, and cerebrovascular events have met with limited success. As much as one-third of cardiovascular mortality can be prevented by abstinence from smoking, an effect that has not yet been realized by pharmaceutical risk-factor management. Effective holistic treatment plans exist for patients who are motivated to cease smoking such as nicotine replacement by transdermal patch or chewable gum, behavioral modification, and antidepressant therapy. However, many physicians do not routinely document smoking behavior or pursue smoking cessation at every clinical encounter, an endeavor that should form part of the standard of care for any patient who endorses an active or recent history of smoking.

6.3 Diabetes mellitus

Coronary artery disease is the principal cause of death in diabetic patients and rivals smoking in contribution to cardiovascular mortality. The rate of coronary and peripheral arterial disease approximately doubles in patients who carry a diagnosis of diabetes. The length of time and severity of diabetic control are strong predictors of atherosclerotic events and have been correlated with the degree of peripheral arterial disease experienced by patients. The microvascular complications of diabetes are beyond the scope of this chapter but diabetic nephropathy, heralded by microalbuminuria, exacerbates large vessel changes imposed by insulin resistance and hyperglycemia. Atherosclerosis can be shown experimentally to be induced by insulin resistance preceding the development of a clinical diagnosis of diabetes and has been diagnosed in adolescents and teenagers as part of the metabolic syndrome.

Significant improvements in the glycemic profile and reduction in diabetic complications with prolongation of life expectancy can be achieved through behavioral modification of diabetes. Level 1 data from large randomized national trials of monitored lifestyle modification demonstrates up to 30% reduction in frank diabetes with associated reduction in cardiovascular events. The addition of effective glycemic agents such as metformin, sulfonylureas, and thiazolidinediones further contribute to cardiovascular risk reduction. Current glucose targets for diabetic patients are listed in Table 2. A causal relationship has been described for long-term blood glucose control as assessed by the Hemoglobin A1c (HbA1c) in the national United Kingdom Prospective Diabetes Study (UKPDS) with an increase in the risk of adverse cardiovascular events for each percentage point above an HbA1c level of 6.2%. The UKPDS recommendations for metabolic control of diabetic patients also
Table 2. Current target guidelines for diabetic patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Target Value</th>
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</thead>
<tbody>
<tr>
<td>Fasting blood glucose</td>
<td>&lt;110 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>LDL</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Triglyceride level</td>
<td>&lt;150 mg/dL</td>
</tr>
</tbody>
</table>

Note: HCTZ = hydrochlorothiazide; ACEI = Angiotensin-converting enzyme; LDL = low-density lipoprotein.

focus on other parameters that are known to interact deleteriously with diabetes to increase cardiovascular risk such as hypertension and hyperlipidemia. Physicians now recognize the need for aggressive management of patients with the constellation of diabetes, hypertriglyceridemia, hypertension, and obesity, some of which will fit the definition of the metabolic syndrome.

6.4 Hypertension

The prevalence of hypertension in the United States is estimated at one in three individuals and rising steadily. Part of the difficulty in managing hypertension is the racial disparity in prevalence, response to antihypertensive medications and associated exacerbating factors such as renal disease and diabetes. High risk groups include African-Americans, those over 60 years of age, and women. A dose phenomenon has been described for hypertension. In general, an elevation in blood pressure of 20 mm Hg systolic from a theorized normal of 120 mm Hg systolic confers a cardiovascular risk double that of the normotensive population. A working definition of hypertension is a systolic blood pressure greater than 140 mm Hg or a diastolic pressure greater than 90 mm Hg. Prehypertension can be defined further as blood pressure ranging between 120 and 139 mm Hg systolic and between 80 and 89 mm Hg diastolic. Traditional views of hypertension primarily focused on diastolic dysfunction and elevation as more significant than the systolic component; however, this perspective has been shifted with more recent data pointing to a greater risk for cardiovascular events and mortality in the face of systolic hypertension. Pulse pressure increases for a given systolic blood pressure have also received more attention as a marker of impairment of vascular receptive relaxation and predict coronary risk over normal controls. Although hypertension is an independent risk factor for the development of coronary disease, it should be noted that it is much more potent
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when considered alongside other commonly associated risk factors such as triglyceride profile, diabetes, and obesity. Almost two-thirds of patients with hypertension have at least one other risk factor for cardiovascular disease and thus treatment of hypertension should be ideally managed by using therapies that are multivariate in effect; for example, dietary modification or pharmacological agents with benefits for both triglyceride and blood pressure profile.

The 2003 Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) panel published guidelines that summarize management goals for the treatment of hypertension-associated risk factors. For example, hyperlipidemia may be more difficult to control when a combination of diuretic and beta-blocking agents is used due to slight alterations in lipid metabolism as a side-effect of these medications. In the presence of diabetes, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and beta-blockers are recommended. Lifestyle modifications are clearly identified with the following JNC-7 guidelines: weight reduction/maintenance of BMI between 18.5 and 24.9 kg/m²; DASH eating plan (dietary approaches to stop hypertension) consisting of a diet rich in fruits, vegetables, low-fat dairy products, low sodium (ideally less than 100 mmol or 6 gm of sodium chloride per day), reduced fat content, moderate alcohol consumption with less than two drinks per day for men and one drink per day for women, and lighter weight individuals; and regular aerobic activity for at least 30 minutes most days of the week.

6.5 Dyslipidemia

LDL is firmly established in cardiovascular risk profiling as the major contributor to atherosclerotic disease and is found in abundance in atherosclerotic plaque. Higher serum levels of LDL correlate to a higher risk of cardiovascular disease; data borne out of clinical studies indicate LDL as the main risk factor for coronary disease. The post-coronary artery bypass graft (Post-CABG) trial examined this relationship further and attempted to define a threshold target level for LDL. The results supported a true risk reduction with intensive LDL treatment to a level lower than 100 mg/dl as evidenced by a favorable change in atherosclerotic plaque morphology (see Table 2).

Although LDL has been identified as a target for cardiovascular risk reduction, there are other lipid and lipoprotein abnormalities that have been recognized in contributing to the overall risk of atherosclerotic disease. Elevated levels of very low density lipoprotein (VLDL), apolipoprotein B, and decreased high density lipoprotein (HDL) are adverse markers for cardiovascular risk. Clinical evidence for the involvement of these lipoproteins is found in the acceleration of atherosclerotic build-up seen in patients suffering from inherited forms of dyslipidemia such as familial hypercholesterolemia.
First-line therapies for reducing cholesterol, LDL, and VLDL and increasing HDL involve behavioral modification in the form of dietary changes. Animal fat including meats and egg yolk are significant sources of cholesterol and goal strategies focus on reduction of cholesterol-rich products by at least 50%. Simply reducing body weight toward goal body mass index will produce significant reductions in LDL levels and reduce the overall cardiovascular risk profile.

The main pharmacological modality employed to impair cholesterol metabolism is the hydroxymethylglutarate coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors or "statin" medications). The mechanism of statin action occurs at the hepatocellular level to inhibit cholesterol synthesis in the liver. Statins are powerfully effective in reducing total body LDL levels (from 30% to 60% depending on dosage). Not surprisingly, these medications have become first-line drug therapy for patients with elevated lipid profiles in the absence of drug contraindications. Myopathy, heralded by a rise in creatine kinase, and transient elevation of hepatic aminotransferases are the most commonly quoted side-effects of statin use. These derangements usually resolve with discontinuation of the medication.

Four other medications deserve brief mention. Ezetimibe is a cholesterol transport inhibitor that acts primarily on the small intestine to reduce cholesterol absorption. Ezetimibe is most effective when combined with statin medications and has been shown to have a synergistic effect on lipid reduction in this setting. Niacin (nicotinic acid) has been demonstrated to be beneficial both in reducing VLDL and LDL and in increasing levels of HDL. Flushing, diarrhea, and a mild diabetogenic effect are all recognized side-effects of niacin use and form the majority of reasons for discontinuation of the medication. Fibric acid derivatives such as Gemfibrozil and Fenofibrate have limited applicability in the primary risk reduction strategy for dyslipidemia as their effect on LDL levels are marginal, however, are of marked benefit in patients with pancreatitis associated with hypertriglyceridemia due to their selective reduction in triglycerides. Bile acid sequestrants are weak cholesterol and LDL lowering medications and act by interrupting the enterohepatic recirculation of bile acids via inhibition of small intestinal bile acid reabsorption.

### 6.6 Metabolic syndrome

Over the past half-century, a constellation of metabolic derangements have been seen more frequently occurring in association. Hypertension, diabetes mellitus, obesity, and dyslipidemia are the four entities most commonly described as part of the metabolic syndrome or colloquially known as Syndrome X. According to the definition drawn up by the 2001 Adult Treatment Panel-III of the National Cholesterol Education Program, metabolic syndrome is diagnosed when three of the following criteria are present.
1. Central obesity (waist circumference >102 cm (M), >88 cm (F)).
2. Fasting plasma glucose >6.1 mmol/L.
3. Hypertension ≥135/85 mmHg or the presence of antihypertensive medications.
4. Dyslipidemia including triglycerides ≥1.7 mmol/L, HDL cholesterol <1.0 mmol/L (M), <1.3 mmol/L (F).

The metabolic syndrome for many of the reasons highlighted earlier in the chapter is strongly associated with the development of cardiovascular disease portending an approximately 2.5 times risk of fatal cardiovascular events in the population. The single most effective treatment for the metabolic syndrome is loss of body weight either by nonsurgical or surgical means, which in almost all cases of dramatic weight loss leads to amelioration of all individual components.

### 6.7 Emerging novel risk factors

Although the above well-established risk factors have been strongly linked to the development of cardiovascular disease, there remains a significant proportion of the atherosclerotic population that does not possess these described risk factors. Searches for other contributing factors have focused on molecular biomarkers as diverse as homocysteine levels, high-sensitivity CRP (hs-CRP), fibrin-degradation products (FDP), and microalbuminuria.

Elevated plasma homocysteine levels have been cited as a defined risk factor for the development of atherosclerotic coronary arterial disease in epidemiological as well as clinical research studies. On a molecular basis, high levels of homocysteine have been demonstrated to occur with disruption of normal methionine metabolism. Homocysteine and related metabolites can be detected in abnormally high levels in the blood and have been linked to an increased risk of stroke, due to carotid plaque buildup, as well as cardiovascular disease. Endothelial damage in association with an alteration of the normal coagulation balance has led to the hypothesis that elevated homocysteine levels directly influence atherogenesis in large vessels. Therapeutic options for individuals diagnosed with homocysteinemia have centered on replacement of vitamin B12 and folic acid as a primary treatment with additional restriction of dietary intake of methionine in vitamin B12-insensitive patients. However, studies have not as of yet shown that lowering homocysteine levels decreases the risk of cardiovascular disease in these patients.

Inflammatory markers such as hs-CRP and FDP have been deemed cardiovascular disease risk-associated and, although originally thought to play a role as potential serum biomarkers of cardiovascular disease, have only been weakly associated with risk stratification and burden of atherosclerotic disease. The relative lack of specificity of these markers dilutes their clinical effect, as many unassociated...
noncardiovascular conditions can cause elevations of either marker. The clinical applicability of these markers has, therefore, been limited and their use in the setting of cardiovascular risk reduction is yet to be elucidated.

High-sensitivity CRP (hs-CRP) has recently been the subject of much attention with the results of the JUPITER trial — a large multinational and double-blind placebo-controlled trial of more than 17,000 people. The trial was designed to observe the effect that treatment with a statin (rosuvastatin) had upon individuals with normal lipid profiles but elevated hs-CRP levels. The study arose from the observation that statins have an anti-inflammatory property and decrease hs-CRP levels in an effect that is independent from their cholesterol-lowering ability. The JUPITER trial demonstrated a reduction in both LDL and hs-CRP levels to around half of pretreatment and was terminated prematurely based on this beneficial result. However, the benefit of a normal hs-CRP has not yet been firmly established as a treatment goal in cardiovascular risk profiling and is additionally confounded by the possible benefit of statin therapy in the face of normal lipid profile in certain populations. Nevertheless, hs-CRP remains an active and controversial area of cardiovascular risk-modification research and its clinical role yet to be formally determined.

Microalbuminuria is a sensitive predictor of mortality and highly associated with cardiovascular adverse events in specific. Diabetic and hypertensive nephropathy can be diagnosed reliably by evidence of proteinuria, which is also associated with an increase in cardiovascular risk profile. Microalbuminuria is similarly associated with an elevated risk of coronary disease, independent of proteinuria, and thus may have clinical utility in patients who do not carry a diagnosis of hypertension or diabetes as a screening tool for atherosclerotic disease. Treatment strategies based upon the detection of microalbuminuria are, therefore, likely to take the form of existing risk-reduction strategies for well-established cardiovascular risk factors.

6.8 Surveillance and secondary prevention

Given the focus on prevention of atherosclerotic disease, increased surveillance for the development of signs of atherosclerotic disease in those with established risk factors should be included in the routine health-care maintenance and follow-up of patients. Regular carotid duplex evaluation for older patients with one or more risk factors for atherosclerosis in addition to at least annual physical examinations is a relatively inexpensive and highly effective screening tool for carotid disease. Similarly, screening aortic ultrasonography, physical examination, and ankle-brachial pressure indices should be considered for at-risk patients in the primary care setting. Electrocardiography and two-dimensional and stress echocardiography are procedures that are best used as diagnostic rather than screening tools; however, their
utility is as a prediction tool for those at the highest risk of cardiovascular disease and may act as the gateway to more invasive diagnostic and treatment options such as angiographic interventions or cardiac surgery.

For those patients who progress to severe or acute cardiovascular disease, secondary prevention guidelines are well documented and rigorously studied. Many cardiovascular centers have established protocols for treating patients with established disease. One such example is the University of California, Los Angeles CHAMP (Cardiovascular Hospitalization Atherosclerosis Management Program), which focuses on employing secondary prevention measures while patients are in the hospital in order to improve clinical outcomes. This program arose through the observation that although evidence-based guidelines for secondary risk prevention are widely disseminated, they are consistently underutilized. The CHAMP guidelines are summarized as follows.

1. Aspirin 81–162 mg daily should be initiated. In the presence of contraindications to aspirin, other platelet agents should be considered, for example, Clopidogrel. Combination therapy can be recommended in the setting of acute coronary syndromes (ACS) or post-revascularization therapy.
2. Statin therapy should be initiated in all patients in the absence of contraindications and in all diabetic patients regardless of their lipid profile. Target levels of LDL should be <70 mg/dL, HDL >40 mg/dL, and triglycerides <150 mg/dL.
3. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARB) should be commenced in the absence of contraindication irrespective of the blood pressure or cardiac ejection fraction.
4. Beta blockade should be prescribed for all patients in the absence of contraindication.
5. Fish oil or omega-3 fatty acids should be commenced with dietary instruction for all patients.
6. Aerobic exercise programs that involve 30–60 minutes of moderately intense exercise at least five times a week should be prescribed.
7. Smoking cessation should be pursued including access to formal smoking cessation programs.
8. Before hospital discharge and at six week follow-up, cardiovascular lipid profile and liver enzymes should be checked and routinely thereafter at future follow-up appointments.

7. Conclusions

As the population ages and becomes more obese, there will be a rise in the number of patients with cardiovascular disease. Aggressive risk-factor modification can only
occur if there is vigilance and attention to the detection and subsequent treatment of such conditions as diabetes, obesity, dyslipidemia, smoking, and renal disease. Although there are many effective strategies for risk reduction, once these conditions have been diagnosed, there is a growing body of epidemiological evidence that points toward greater health outcomes when the predisposing factors for these diseases are addressed early, prior to full blown disease diagnosis.

Preventing individuals from becoming smokers rather than focusing on smoking cessation and educating individuals about diet and exercise strategies to prevent obesity and modulation of cholesterol intake to reduce hyperlipidemia are all paradigms for reducing the exposure of the population to cardiovascular risk factors. Unfortunately, patients have not embraced these preventative strategies and public health measures have not been successful in a cost-effective and widespread manner at the present time.

Cardiovascular disease continues to be the most significant cause of mortality in the United States and similarly developed countries. The detection of modifiable risk factors for atherosclerosis continues to remain one of the most promising areas of research in the field of cardiovascular medicine. Despite advances in pharmacological treatment of identified risk factors, however, behavioral modification strategies that are effective are limited. Attitude toward health and cultivation of risk-factor avoidance has been difficult to implement; however, these attributes are most likely to reduce the burden of cardiovascular disease most significantly. These core health traits must be adopted by individuals themselves and supported by education and demonstration of identifiable health benefit before prevention of cardiovascular disease can be entertained at a population level.

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