VITEBSK STATE MEDICAL UNIVERSITY

CHAIR OF THE FACULTY THERAPY

**FACULTY THERAPY**

(Methodics work out for foreign students, studying the course of faculty therapy)

Part 1

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**ATHEROSCLEROSIS**

Atherosclerosis is a disease of large and medium-sized muscular arteries and is characterized by endothelial dysfunction, vascular inflammation, and the buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall. This buildup results in plaque formation, vascular remodeling, acute and chronic luminal obstruction, abnormalities of blood flow, and diminished oxygen supply to target organs.

**Frequency**

The true frequency of atherosclerosis is difficult, if not impossible, to accurately determine because it is a predominantly asymptomatic condition. The process of atherosclerosis begins in childhood with the development of fatty streaks. These lesions can be found in the aorta shortly after birth and appear in increasing numbers in those aged 8-18 years. More advanced lesions begin to develop when individuals are aged approximately 25 years. Subsequently, an increasing incidence of the advanced complicated lesions of atherosclerosis exists, and the organ-specific clinical manifestations of the disease increase with age through the fifth and sixth decades of life.

In the United States, approximately 1.5 million myocardial infarctions occur annually, and more than 11 million Americans have chronic coronary artery disease. Of persons older than 50 years, 30% have some evidence of carotid artery disease, and cerebrovascular disease is responsible for over 200,000 deaths per year in the United States.

The incidence of clinical manifestations of atherosclerosis in Great Britain, west of Scotland in particular, is especially high. The same is true of Finland, in particular, and Scandinavia in general. Russia and many of the former states of the Soviet Union recently have experienced an exponential increase in the incidence of coronary heart disease that likely is the result of widespread economic hardship and social upheaval, a high prevalence of cigarette habituation, and a diet high in saturated fats. The incidence of coronary heart disease in the Far East is significantly lower than the incidence documented in the West. Ill-defined genetic reasons for this phenomenon may exist, but significant interest surrounds the role of diet and other environmental factors in the absence of clinical atherosclerotic vascular disease in these populations.

The incidence of coronary artery disease in ethnic immigrant populations in the United States approaches the incidence of disease in whites, supporting the role of these putative environmental factors. Atherosclerotic cardiovascular disease also is rare on the African continent, although growing evidence indicates that this too is changing as a result of rapid westernization and urbanization of the traditionally rural and agrarian African populations.

Atherosclerosis is the leading cause of death in the developed world, and atherosclerosis is predicted to be the leading cause of death in the developing world within the first quarter of the next century.

Atherosclerosis is responsible for more than half of the yearly mortality in the United States, and more than 500,000 people die annually of myocardial infarction alone. This rate of mortality costs the country more than $100 billion a year. More than 50 million people in the United States are candidates for some form of dietary and/or drug treatment to modify their lipid profile.

Atherosclerosis is more common among men than women. The higher prevalence of atherosclerosis in men is thought to be due to the protective effects of the female sex hormones. This sex effect is absent after menopause in women. The incidence of coronary heart disease among women parallels that of men, but women demonstrate an approximately 10-year chronological delay in the onset of clinical manifestations.

Age: Most cases of atherosclerotic vascular disease become clinically apparent in patients aged 40-70 years.

**Atherosclerosis - Theories of genesis**

**The encrustation theory**

This theory, proposed by Rokitansky in 1851, suggested that atherosclerosis begins in the intima with deposition of thrombus and its subsequent organization by the infiltration of fibroblasts and secondary lipid deposition.

**The lipid theory**

In 1856, Virchow proposed that atherosclerosis starts with lipid transudation into the arterial wall and its interaction with cellular and extracellular elements, causing "intimal proliferation."

**The response-to-endothelial injury theory**

Ross proposed this more unifying theory. Termed the response-to-injury hypothesis, it postulates that atherosclerosis begins with endothelial injury, making the endothelium susceptible to the accumulation of lipids and the deposition of thrombus.

**The currently accepted response-to-vascular injury theory**

Over the past decade, Fuster and colleagues have proposed that vascular injury starts the atherosclerotic process. The effect of such vascular injury can be classified as follows:

Type I - Vascular injury involving functional changes in the endothelium with minimal structural changes, (ie, increased lipoprotein permeability and white blood cell adhesion)

Type II - Vascular injury involving endothelial disruption with minimal thrombosis

Type III - Vascular injury involving damage to media, which may stimulate severe thrombosis, resulting in unstable coronary syndromes

According to the response-to-vascular injury theory, injury to the endothelium by local disturbances of blood flow at angulated or branch points, along with systemic risk factors (eg, hyperglycemia, dyslipidemia, cigarette smoking, possibly infection) perpetuates a series of events that culminate in the development of atherosclerotic plaque.

**Role of endothelium**

Endothelium is the monolayered inner lining of the vascular system. It covers almost 700 m2 and weighs 1.5 kg.

Functions of endothelium

* Providing a nonthrombogenic surface. This is achieved by producing prostaglandin derivatives such as prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, and by its surface covering of heparan sulfate.
* Secreting the most potent vasodilator, EDRF, a thiolated form of nitric oxide: EDRF formation by endothelium is critical in maintaining a balance between vasoconstriction and vasodilation in the process of arterial homeostasis.
* Secreting agents effective in lysing fibrin clots: These agents include plasminogen and procoagulant materials such as von Willebrand factor and type 1 plasminogen activator inhibitor.
* Secreting various cytokines and adhesion molecules, such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1
* Secreting a number of vasoactive agents, such as endothelin, angiotensin II (A-II), serotonin, and platelet-derived growth factor, which may be important in vasoconstriction.

Endothelium, through the above mechanisms, regulates the following:

* Vascular tone
* Platelet activation
* Monocyte adhesion and inflammation
* Thrombus generation
* Lipid metabolism
* Cellular growth and vascular remodeling

Endothelial damage occurs in many clinical settings and can be demonstrated in individuals with dyslipidemia, hypertension, diabetes, advanced age, nicotine exposure, and products of infective organisms (ie, Chlamydia pneumoniae). Experimental studies have shown that endothelial damage may be reversed if the underlying cause is attenuated. Endothelial damage may cause changes that are localized or generalized and transient or persistent, as follows:

* Increased permeability to lipoproteins
* Decreased nitric oxide production
* Increased leukocyte migration and adhesion
* Prothrombotic dominance
* Vascular growth stimulation
* Vasoactive substance release

Endothelial dysfunction is the initial step that allows diffusion of lipids and inflammatory cells (ie, monocytes, T lymphocytes) into the endothelial and subendothelial spaces. Secretion of cytokines and growth factors promotes intimal migration; SMC proliferation; and accumulation of collagen matrix, monocytes, and other white blood cells, forming an atheroma. More advanced atheromas, even though nonocclusive, may rupture, thus leading to thrombosis and the development of ACS and MI.

Multiple studies have demonstrated that risk-factor modification through therapeutic lifestyle change (TLC), reduction of low-density lipoprotein cholesterol (LDL-C) levels, and smoking cessation rapidly improves endothelial function.

**The role of infection**

Traditional risk factors, such as dyslipidemia, tobacco abuse, hypertension, and diabetes, often do not account for atherosclerosis in many patients. Certain nontraditional risk factors, including hyperhomocystinemia, are sometimes blamed. However, accumulating evidence suggests that atherosclerosis is an inflammatory disease; therefore, a great deal of attention has recently been focused on the possibility that infectious agents play a role in the etiology of CAD. Certain infectious agents have been implicated based on their isolation from the atheromatous plaques or on the presence of positive serology findings for organisms such as C pneumoniae, Helicobacter pylori, herpes simplex virus, and cytomegalovirus.

**Causes**

A number of large epidemiological studies in North America and Europe have identified numerous risk factors for the development and progression of atherosclerosis.

The risk factors can be divided into **modifiable and nonmodifiable** risk factors and include:

**Nonmodifiable**

Family history of premature CAD

Age

Sex

**Modifiable**

Hypercholesterolemia (high LDL syndrome)

Hypertension

Cigarette smoking

Diabetes mellitus

Hypoalphalipoproteinemia

Dysmetabolic syndrome

Obesity

Physical inactivity

**Nontraditional risk factors**

Hyperhomocystinemia

High lipoprotein(a) levels

High iron levels

Syndromes of accelerated atherosclerosis - Graft atherosclerosis, CAD after cardiac transplantation

Restenosis

Infection

C pneumoniae

H pylori

Herpes simplex virushyperlipidemia

More recently, a number of novel risk factors have been identified that add to the predictive value of the established risk factors and may prove to be a target for future medical interventions.

* Hyperlipidemia is an established risk factor for atherosclerosis. Convincing evidence that lowering serum cholesterol reduces the risk of subsequent coronary heart disease events and overall mortality exists.
* Hypertension is a risk factor for the development of atherosclerosis, atherosclerotic cardiovascular disease, and stroke.

Hypertension is associated with morphologic alterations of the arterial intima and functional alterations of the endothelium that are similar to the changes observed in hypercholesterolemia and established atherosclerosis. *Endothelial dysfunction is a feature of hypertension, hyperlipidemia, and atherosclerosis and is known to represent and contribute to the procoagulant, proinflammatory, and proliferative components of atherogenesis*.

* Diabetes mellitus - an important risk factor for hyperlipidemia and atherosclerosis and commonly associated with

hypertension,

abnormalities of coagulation,

platelet adhesion and aggregation,

increased oxidative stress,

functional and anatomic abnormalities of the endothelium and endothelial vasomotion.

* Cigarette habituation - a major and modifiable risk factor for atherosclerosis and is associated with an increased relative risk of dying from vascular disease.

The mechanisms are complex and likely multifactorial and result in endothelial dysfunction and a relatively hypercoagulable state. This increased relative risk rapidly and significantly is reduced with smoking cessation. The relative risk is reduced to the extent that the incidence of coronary heart disease in people who have recently quit smoking is similar to that of people who have not smoked for at least 2 years.

Novel risk factors: The established risk factors noted above successfully predict future cardiac events in about 50-60% of patients. In recent years, a concerted effort to identify and validate new markers of future risk of the clinical consequences of atherosclerosis has been made.

* C-reactive protein. Baseline C-reactive protein (CRP) levels add to the predictive value of lipid parameters in determining the risk of first myocardial infarction in apparently healthy men and women without a history of coronary heart disease.

CRP reflects systemic inflammation, and these results support the hypothesis that chronic inflammation may play a role in the pathogenesis and progression of atherosclerosis.

* Homozygous hyperhomocystinemia is associated with extensive atherosclerosis at an early age.

The inherited enzymatic abnormalities of homocysteine metabolism that result in such abnormal levels of the amino acid fortunately are very rare.

Atherogenesis due to hyperhomocystinemia likely is due to oxidative damage to the endothelium followed by platelet activation and thrombus formation.

* Fibrinogen may be elevated in association with risk factors for atherosclerosis, including smoking, age, and diet; however, recent evidence suggests that elevated levels of fibrinogen are a strong independent predictor of future cardiovascular events in apparently healthy patients and patients with a prior history of cardiovascular disease. This association may be as strong as the established association between hypercholesterolemia and coronary heart disease.
* Lipoprotein (a). Numerous studies have linked elevated plasma levels of lipoprotein (a), an LDL-like moiety that circulates in the blood attached to apolipoprotein (a), with the development of coronary artery disease. This complex shares structural domains with the fibrinolytic enzyme plasminogen and may render the molecule prothrombotic.

**Pathophysiology**

A complex and incompletely understood interaction exists between the critical cellular elements of the atherosclerotic lesion. These cellular elements are endothelial cells, smooth muscle cells, platelets, and leucocytes. Vasomotor function, the thrombogenicity of the blood vessel wall, the state of activation of the coagulation cascade, the fibrinolytic system, smooth muscle cell migration and proliferation, and cellular inflammation are complex and interrelated biological processes that contribute to atherogenesis and the clinical manifestations of atherosclerosis.

The mechanisms of atherogenesis remain uncertain.

The ”response-to-injury” theory is most widely accepted.

* Endothelial injury causes vascular inflammation and a fibroproliferative response ensues.
* Probable causes of endothelial injury include

 oxidized low-density lipoprotein (LDL) cholesterol;

infectious agents;

toxins, including the byproducts of cigarette smoking;

hyperglycemia;

hyperhomocystinemia.

* Circulating monocytes infiltrate the intima of the vessel wall, and these tissue macrophages act as scavenger cells, taking up LDL cholesterol and forming the characteristic foam cell of early atherosclerosis. These activated macrophages produce numerous factors that are injurious to the endothelium.
* Elevated serum levels of LDL cholesterol overwhelm the antioxidant properties of the healthy endothelium and result in abnormal endothelial metabolism of this lipid moiety. Oxidized LDL is capable of a wide range of toxic effects and cell/vessel wall dysfunctions that are characteristically and consistently associated with the development of atherosclerosis.
* These dysfunctions include impaired endothelium-dependent dilation and paradoxical vasoconstriction. These dysfunctions are the result of direct inactivation of nitric oxide by the excess production of free radicals, reduced transcription of nitric oxide synthase messenger RNA (mRNA), and posttranscriptional destabilization of mRNA.
* The decrease in the availability of nitric oxide also is associated with increased platelet adhesion, increased plasminogen activator inhibitor, decreased plasminogen activator, increased tissue factor, decreased thrombomodulin, and alterations in heparan sulfate proteoglycans. The consequences include a procoagulant milieu and enhanced platelet thrombus formation. Furthermore, oxidized LDL activates inflammatory processes at the level of gene transcription by up-regulation of nuclear factor kappa-B, expression of adhesion molecules, and recruitment of monocytes/macrophages.

The lesions of atherosclerosis do not occur in a random fashion.

* **Hemodynamic factors** interact with the activated vascular endothelium. Fluid shear stresses generated by blood flow influence the phenotype of the endothelial cells by modulation of gene expression and regulation of the activity of flow-sensitive proteins.
* Atherosclerotic plaques characteristically occur in regions of branching and marked curvature at areas of geometric irregularity and where blood undergoes sudden changes in velocity and direction of flow.
* Decreased shear stress and turbulence may promote atherogenesis at these important sites within the coronary arteries, the major branches of the thoracic and abdominal aorta, and the large conduit vessels of the lower extremities.

**Histopathology of atherosclerotic lesions**

Stary I lesion: The endothelium also expresses surface adhesion molecules E selectin and P selectin, attracting more polymorphonuclear cells and monocytes in the subendothelial space.

Stary II lesion: Macrophages begin to take up large amounts of LDL (fatty streak).

Stary III lesion: As the process continues, macrophages eventually become foam cells.

Stary IV lesion: Lipid exudes into the extracellular space and begins to coalesce to form the lipid core.

Stary V lesion: SMCs and fibroblasts move in, forming fibroatheromas with soft inner lipid cores and outer fibrous caps.

Stary VI lesion: Rupture of the fibrous cap with resultant thrombosis causes ACS.

Stary VII and VIII lesions: As lesions stabilize, they become fibrocalcific (Stary VII lesion) and, ultimately, fibrotic with extensive collagen content (Stary VIII lesion).

Atherosclerotic plaque may require 10-15 years for full development. Further growth is determined by the local activity of regulatory substances (ie, interleukin (IL)–1, IL-6, transforming growth factor-beta) and by thrombin, leukotriene, prostaglandin, fibrin, and fibrinogen.

* 1. The earliest pathologic lesion of atherosclerosis is the fatty streak.
* The fatty streak is observed in the aorta and coronary arteries of most individuals by age 20 years.
* The fatty streak is the result of focal accumulation of serum lipoproteins within the intima of the vessel wall.
* Microscopy reveals lipid-laden macrophages, T lymphocytes, and smooth muscle cells in varying proportions.
* The fatty streak may progress to form a fibrous plaque, the result of progressive lipid accumulation and the migration and proliferation of smooth muscle cells.

 Platelet-derived growth factor,

 insulinlike growth factor,

transforming growth factors alpha and beta,

 thrombin,

 angiotensin II

are potent mitogens that are produced by activated platelets, macrophages, and dysfunctional endothelial cells that characterize early atherogenesis, vascular inflammation, and platelet-rich thrombosis at sites of endothelial disruption.

2. The relative deficiency of endothelium-derived nitric oxide further potentiates this proliferative stage of plaque maturation.

3. These smooth muscle cells are responsible for the deposition of extracellular connective tissue matrix and **form a fibrous cap** that overlies a core of lipid-laden foam cells, extracellular lipid, and necrotic cellular debris.

4. Growth of the fibrous plaque results in vascular remodeling, progressive luminal narrowing, blood-flow abnormalities, and compromised oxygen supply to the target organ.

 Human coronary arteries enlarge in response to plaque formation, and luminal stenosis may only occur once the plaque occupies greater than 40% of the area bounded by the internal elastic lamina.

Denudation of the overlying endothelium or rupture of the protective fibrous cap may result in exposure of the thrombogenic contents of the core of the plaque to the circulating blood. This exposure constitutes an advanced or complicated lesion. The plaque rupture occurs due to weakening of the fibrous cap. Inflammatory cells localize to the shoulder region of the vulnerable plaque. T lymphocytes elaborate interferon gamma, an important cytokine that impairs vascular smooth muscle cell proliferation and collagen synthesis. Furthermore, activated macrophages produce matrix metalloproteinases that degrade collagen. These mechanisms explain the predisposition to plaque rupture and highlight the role of inflammation in the genesis of the complications of the fibrous atheromatous plaque. A plaque rupture may result in thrombus formation, partial or complete occlusion of the blood vessel, and progression of the atherosclerotic lesion due to organization of the thrombus and incorporation within the plaque.

**CLINICAL**

**History**

The symptoms of atherosclerosis are highly variable.

Patients with mild atherosclerosis may present with clinically important symptoms and signs of disease and myocardial infarction, or sudden cardiac death may be the first symptom of coronary heart disease.

However, many patients with anatomically advanced disease may have no symptoms and experience no functional impairment. Initially thought to be a chronic, slowly progressive, degenerative disease, it is now apparent that atherosclerosis is a disease with periods of activity and quiescence. Although a systemic disease, atherosclerosis manifests in a focal manner and affects different organ systems in different patients for reasons that remain unclear.

Progressive luminal narrowing of an artery due to expansion of a fibrous plaque results in impairment of flow once more than 50-70% of the lumen diameter is obstructed. This impairment in flow results in symptoms of inadequate blood supply to the target organ in the event of increased metabolic activity and oxygen demand. Stable angina pectoris, intermittent claudication, and mesenteric angina are examples of the clinical consequences of this mismatch.

Rupture of a plaque or denudation of the endothelium overlying a fibrous plaque may result in exposure of the highly thrombogenic subendothelium and lipid core. This exposure may result in thrombus formation, which may partially or completely occlude flow in the involved artery. Unstable angina pectoris, myocardial infarction, transient ischemic attack, and stroke are examples of the clinical sequelae of partial or complete acute occlusion of an artery. Atheroembolism is a distinct clinical entity that may occur spontaneously or as a complication of aortic surgery, angiography, or thrombolytic therapy in patients with advanced and diffuse atherosclerosis.

1. **Angina pectoris** is characterized by retrosternal chest discomfort that typically radiates to the left arm and may be associated with dyspnea. Angina pectoris is exacerbated by exertion and relieved by rest or nitrate therapy. Unstable angina pectoris describes a pattern of increasing frequency or intensity of episodes of angina pectoris and includes pain at rest. A prolonged episode of angina pectoris that may be associated with diaphoresis is suggestive of myocardial infarction.
2. **Stroke**, reversible ischemic neurological deficit, and transient ischemic attack are a range of manifestations of impairment of vascular supply to the central nervous system and are characterized by the sudden onset of a focal neurological deficit of variable duration, respectively.
3. **Peripheral vascular disease** typically manifests as intermittent claudication, impotence, and nonhealing ulceration and infection of the extremities. Intermittent claudication describes calf, thigh, or buttock pain that is exacerbated by exercise and relieved by rest. Intermittent claudication may be accompanied by pallor of the extremity and paresthesias.
4. **Visceral ischemia** may be occult or symptomatic prior to symptoms and signs of target organ failure.
5. **Mesenteric angina** is characterized by epigastric or periumbilical postprandial pain and may be associated with hematemesis, hematochezia, melena, diarrhea, nutritional deficiencies, and weight loss.
6. **Abdominal aortic aneurysm** typically is asymptomatic prior to the dramatic and often fatal symptoms and signs of rupture, although patients may describe a pulsatile abdominal mass.
7. **Atheroembolism** may present with symptoms of digital necrosis, gastrointestinal bleeding, myocardial infarction, retinal ischemia, cerebral infarction, and renal failure.

**Physical**

The physical signs of atherosclerosis provide objective evidence of extracellular lipid deposition, stenosis or dilatation of large muscular arteries, or target organ ischemia or infarction.

* Hyperlipidemia - Xanthelasma, tendon xanthomata
* Coronary artery disease - Fourth heart sound, tachycardia, hypotension, hypertension
* Cerebrovascular disease - Diminished carotid pulses, carotid artery bruits, focal neurological deficits
* Peripheral vascular disease - Decreased peripheral pulses, peripheral arterial bruits, pallor, peripheral cyanosis, gangrene, ulceration
* Abdominal aortic aneurysm - Pulsatile abdominal mass, peripheral embolism, circulatory collapse
* Atheroembolism - Livedo reticularis, gangrene, cyanosis, ulceration (The presence of pedal pulses in the setting of peripheral ischemia suggests microvascular disease and includes cholesterol embolization.)

**Lab Studies**

* Routine blood tests
* CBC count
* Chemistry panel (glucose)
* Thyroid function tests - To exclude thyroid disorders
* Fasting lipid profile

Total cholesterol level

LDL-C level

HDL cholesterol (HDL-C) level

Triglyceride level

* Special tests

Specific lipid studies (if necessary)

Small, dense LDL-C level

Lipoprotein(a) level

Apoprotein profile

Homocysteine level

* Inflammatory markers (eg, CRP)
* Tests specific to the presentation of ACS (Serum markers)

Creatine kinase with MB isozymes

Troponins (I or T)

Lactate dehydrogenase and lactate dehydrogenase isozymes

Serum aspartate aminotransferase

Inflammatory markers - CRP

* Measuring any number of parameters that may reflect inflammation, coagulation, fibrinolytic status, and platelet aggregability is possible.

**Imaging Studies**

* Ultrasound aids in evaluating brachial artery reactivity and carotid artery intima-media thickness, which are measures of vessel wall function and anatomy, respectively. These evaluations remain research techniques at this time but hold promise as reliable noninvasive, and therefore repeatable, measures of disease and surrogate end-points for the evaluation of therapeutic interventions.
* Carotid artery intima-media thickness: B-mode ultrasonography of the common and internal carotid arteries is a noninvasive measure of arterial wall anatomy that may be performed repeatedly and reliably in asymptomatic individuals. The combined thickness of the intima and media of the carotid artery is associated with the prevalence of cardiovascular risk factors and disease and an increased risk of myocardial infarction and stroke. This association is at least as strong as the associations observed with traditional risk factors.

**Medical Care**

 The prevention and treatment of atherosclerosis requires control of the known modifiable risk factors for this disease. This includes the medical treatment of hypertension, hyperlipidemia, diabetes mellitus, and cigarette habituation.

* Hypertension is a risk factor for the development of atherosclerosis, atherosclerotic cardiovascular disease, and stroke.

The mechanism by which hypertension causes these effects is not known, and some uncertainty exists as to what the primary and secondary factors are in a typically multifactorial syndrome. These factors may include hyperlipidemia, hypertension, diabetes mellitus, obesity, and physical inactivity.

Dietary and pharmacological treatment of hypertension is associated with a decreased incidence of stroke and, to a lesser degree, atherosclerotic cardiovascular disease.

* Convincing evidence that lowering serum cholesterol reduces the risk of subsequent coronary heart disease events and overall mortality exists.

The HMG-CoA reductase inhibitors inhibit the rate-limiting step of cholesterol synthesis in the liver. HMG-CoA reductase inhibitors are effective in lowering the serum total cholesterol, LDL cholesterol, and triglyceride levels and in raising the serum HDL cholesterol level, and they have a low incidence of adverse effects, the most common being hepatotoxicity and myopathy.

The success of the HMG-CoA reductase inhibitors in reducing circulating lipid levels and improving the clinical and anatomic course of atherosclerosis has focused attention on the management of hyperlipidemia. In addition, an important role remains for other hypolipidemic agents that may be of particular benefit for patients with refractory LDL hypercholesterolemia, hypertriglyceridemia, low HDL cholesterol, and elevated lipoprotein (a).

* Primary prevention of coronary artery disease
	1. Cholesterol lowering with the HMG-CoA reductase inhibitors has yielded important reductions in coronary heart disease events in patients with diabetes mellitus.
	2. The benefit of strict glycemic control in the prevention of macrovascular disease has been difficult to confirm, although this intuitively is beneficial and is known to retard the progression of microvascular disease.
	3. The risks of cigarette smoking are reduced rapidly and significantly with smoking cessation. The relative risk is so significant that the incidence of coronary heart disease in people who have recently quit smoking is similar to that of people who have not smoked within 2 years.
	4. The primary treatment of LDL hypercholesterolemia is dietary and includes restriction of caloric intake, saturated fats, and cholesterol. The NCEP and the American Heart Association (AHA) made specific recommendations for dietary therapy for coronary heart disease prevention. The recommended daily intake of nutrients is described by the step I and step II diets and is appropriately tailored to the level of coronary heart disease risk.
	5. Moderate alcohol intake is associated with a reduced incidence of coronary heart disease events. The mechanism(s) of this benefit is not well understood. Heavy alcohol intake probably is associated with an increased incidence of coronary heart disease events, as well as cardiomyopathy and arrhythmia and obviously should be discouraged.
	6. Physical inactivity is a minor modifiable risk factor for coronary heart disease, and regular exercise has been shown to reduce the risk of coronary heart disease in a number of observational epidemiological studies. The mechanisms for this apparent benefit may include an increase in HDL cholesterol and a decrease in body weight, insulin resistance, and blood pressure. The optimal intensity and duration of exercise is not known; however, 20-30 minutes of aerobic exercise of mild-to-moderate intensity (including walking) 3 times per week probably is appropriate.

**MEDICATION**

Prevention and treatment of atherosclerosis requires risk factor control, including the medical treatment of hypertension, diabetes mellitus, and cigarette habituation.

Advances in the understanding of the vascular biology of atherosclerosis raises the possibility of novel therapies that may address more directly the various aspects of endothelial dysfunction and the role of endothelial dysfunction in atherogenesis. Potential cellular targets include vascular smooth muscle cells, monocyte/macrophage cell lines, platelets, and endothelial cells. Evidence exists that antiplatelet agents, antioxidant therapies, amino acid supplementation, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers may prove to prevent or slow the progression of the disease.