

The Pathology of Atherosclerosis: Plaque Development and Plaque Responses to Medical Treatment

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ABSTRACT

Atherosclerosis develops over the course of 50 years, beginning in the early teenage years. The causes of this process appear to be lipid retention, oxidation, and modification, which provoke chronic inflammation at susceptible sites in the walls of all major conduit arteries. Initial fatty streaks evolve into fibrous plaques, some of which develop into forms that are vulnerable to rupture, causing thrombosis or stenosis. Erosion of the surfaces of some plaques and rupture of a plaque's calcific nodule into the artery lumen also may trigger thrombosis. The process of plaque development is the same regardless of race/ethnicity, sex, or geographic location, apparently worldwide. However, the rate of development is faster in patients with risk factors such as hypertension, tobacco smoking, diabetes mellitus, obesity, and genetic predisposition. Clinical trial data demonstrate that treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) favorably alters plaque size, cellular composition, chemical composition, and biological activities centered on inflammation and cholesterol metabolism, as well as the risk of clinical events due to atherosclerosis. Even with advanced atherosclerosis, statins begin to improve clinical risk within 4 months. During long-term follow-up in clinical trials for up to 11 years with or without further treatment, clinical benefit remains significant, indicating the durability of treatment-induced changes in the development of plaque. Thus, atherosclerosis, a disease heretofore viewed as inevitably progressive, can be treated to significantly alter arterial lesions and reduce their clinical consequences.

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The clinical practitioner's goal for atherosclerosis is to treat it effectively. The purpose of this article is to introduce the pathology of atherosclerotic lesions to provide a rational basis for their clinical management. For each human individual, the natural history of the pathology of arterial lesion development lasts >40 years.^{1,2} Treatments such as diet modification, exercise, and drugs that affect plasma lipids and hypertension may induce changes in the clinical manifestations and in the natural pathology of plaques and arteries.

This review of plaque pathology includes a discussion of both gross pathology and histopathology, along with information on assessment of plaques by various imaging meth-

ods, because some significant pathology is currently described indirectly only by clinical imaging methods. These imaging methods have been rigorously validated and calibrated against the standard of classic histopathologic methods applied directly to human tissues, and sometimes are referred to as "virtual histology."

Definitions of the terms used in this article are provided in Table 1.

WHAT IS ATHEROSCLEROSIS? HOW DO WE STUDY IT?

Atherosclerosis is a disease of the arterial wall that occurs at susceptible sites in the major conduit arteries. It is initiated by lipid retention, oxidation, and modification, which provoke chronic inflammation, ultimately causing thrombosis or stenosis. Atherosclerotic lesions can cause stenosis with potentially lethal distal ischemia or can trigger thrombotic occlusion of major conduit arteries to the heart, brain, legs,

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Table 1 Glossary of terms

Term	Definition
Atheroma	Accumulation of cells or cellular debris that contain lipids, calcium, and fibrous connective tissue between the endothelium lining and the smooth muscle cell-rich medial wall of arteries
Fatty streak	The first grossly visible lesion in the development of atherosclerosis
Fibrous cap	A layer of fibrous connective tissue in the intima
Foam cells	Cells in an atheroma that consist of monocyte macrophages containing numerous lipid inclusions rich in cholesteryl esters
Intima	The innermost layer of a blood vessel
Intimal thickening	Accumulation in the intima of smooth muscle cells within a matrix of proteoglycans
Plaque	Accumulation of fatty deposits within the wall of a blood vessel
Thin-cap fibroatheroma (TCFA)	A thin fibrous cap infiltrated with macrophages and lymphocytes, rare smooth muscle cells, and an underlying lipid-rich necrotic core
Vulnerable plaque	A plaque whose thin fibrous cap is prone to rupture and cause thrombosis

and other organs. Lesions begin in the inner lining of the arteries—the intima—and they progressively affect the entire arterial wall, including the media and the adventitia. Atherosclerosis has been a human disease for >3,500 years; it occurred in Egyptian mummies and showed the same pathologic features that are observed in modern times.³ Several risk factors may intensify or provoke atherosclerosis through their effects on low-density lipoprotein (LDL) particles and inflammation. These risk factors most frequently include hypertension, tobacco smoking, diabetes mellitus, obesity, and genetic predisposition; the molecular details of how they work are not yet known.

Our knowledge of the major characteristics of human atherosclerosis is based largely on studies of coronary artery lesions, with significant contributions from studies of closely similar lesions in the carotid arteries and aorta. Studies of experimental atherosclerosis in various animal species, particularly in genetically manipulated mice, have identified contributions from components of lipid metabolism, components of the inflammatory response, and various cell types within the lesion.^{4–6} These animal studies have demonstrated that inflammatory processes tightly regulate the developmental processes of lesions, with significant contributions from both adaptive and innate immune processes.^{7–10}

ATHEROSCLEROSIS: A GRADUAL, LIFELONG CONTINUUM OF CHANGES IN ARTERIAL TISSUES

Atherosclerosis develops progressively through continuous evolution of arterial wall lesions centered on the accumulation of cholesterol-rich lipids and the accompanying inflammatory response. These changes have been described in the histopathology of human plaques and the plaques of experimental animals. These systematically observed changes are closely similar in the coronary arteries, the carotid arteries, and the aorta, and they form a strong description of the total cumulative development of atherosclerosis.

As development progresses with lipid accumulation and inflammation, the processes and histologic changes become increasingly complex and can vary considerably among individuals and within any given individual. In the natural course of atherosclerosis, spontaneous regression of early-stage lesions may occur, but the intermediate and advanced stages appear to be continuously progressive. This concept of a developmental continuum of plaque changes is useful as an aid to understanding the potential steps of atherosclerosis development. Although our current molecular understanding of these steps and their integration is fragmentary, their general outline supports crucial interplay among lipid accumulation, lipid oxidation, and inflammation.

The continuous development of atherosclerosis usually is described in 2 ways that are different but complementary: (1) as an extended series of histologic processes and changes, and (2) as a shorter series of different classes of lesions that are grossly visible to the unaided eye. Together, these approaches enhance our understanding of atherosclerosis. Both are clinically useful when combined with clinical imaging of plaques for diagnosing each individual patient's stage of atherosclerosis and risks, and for selecting appropriate therapy.

UNDERSTANDING THE DEVELOPMENT OF ATHEROSCLEROSIS AS A CONTINUUM OF HISTOLOGIC CHANGES IN THE ARTERIAL WALL

Natural variation in the rate and extent of development causes marked heterogeneity in plaque histology within individual plaques, among adjacent plaques, among different arteries, and among individual patients. See [Figure 1](#) for examples of the histologic complexity of lesions.^{11–13}

Major changes in the development of atherosclerotic plaques are described briefly in the next paragraphs in their approximate order of occurrence to illustrate their range of complexity and extent.

Early Fatty Streak Development

Early fatty streak development begins in childhood and adolescence.^{11,14,15}

The initial step occurs when LDL particles leave the blood and enter the arterial intima, where, if LDL levels are increased, they accumulate. They then are modified by enzymes and are oxidized into proinflammatory particles, which provoke the reaction of the innate inflammatory system within the intima. Fat droplets may accumulate in the cytoplasm of smooth muscle cells. These first changes in the arterial wall occur at the branch points of arteries, where adaptive intimal thickening occurs in response to normal hemodynamic stresses.

Inflammation begins when the endothelial cells become activated and secrete adhesion molecules, and the smooth muscle cells secrete chemokines and chemoattractants, which together draw monocytes, lymphocytes, mast cells, and neutrophils into the arterial wall. Intimal smooth muscle cells also secrete into the extracellular matrix proteoglycans, collagen, and elastic fibers.

Upon entry, monocytes transform into macrophages, take up lipids as multiple small inclusions, and become foam cells. The degree of lipid accumulation is critical for early-stage diagnosis of atherosclerosis. Isolated foam cells, multiple layers of foam cells, and isolated extracellular pools of lipid are not considered atherosclerosis. These early changes are microscopic and may progress to gross visibility. These lipid changes can be reversed. Atherosclerosis is believed to start when the lipid accumulation appears as confluent extracellular lipid pools and extracellular lipid cores with decreased cellularity.

Early Fibroatheroma

Early fibroatheroma occurs in persons in their teens and 20s.^{11–13,16} Numerous macrophage foam cells, other activated inflammatory cells, and the natural cells of arteries accumulate. Macrophages take a controlling role in plaque development, but inflammation may become unchecked and excessive. Extracellular proteoglycans, secreted by smooth muscle cells, bind lipids and progressively increase their lipid-binding capacity by extension of their disaccharide arms. Some factors promote the death of macrophages and smooth muscle cells. The necrotic debris provokes further inflammation.

Increasing accumulation of extracellular lipid coalesces into pools and causes cell necrosis. This progressively distorts the normal architecture of the intima until it is completely disrupted. These enlarging pools form lipid-rich necrotic cores that dominate the central part of the intima, ultimately occupying 30% to 50% of arterial wall volume.

Fibrous tissue is added to form a fibrous cap over the lipid-rich necrotic cores and just under the endothelium at the blood interface. This forms the fibrous plaque lesions that develop to become the dominant lesion. See [Figure 1A](#) for this development in the natural history of atherosclerosis,

starting at about age 15 to 30 years and continuing throughout life.

Advancing Atheroma: Thin-Cap Fibroatheroma and Its Rupture

Advancing atheroma occurs in persons aged ≥ 55 years. In this stage of plaque development, a thin-cap fibroatheroma (TCFA) develops and may rupture.^{12,17,18}

The fibrous cap at a few sites becomes thin and weakened when proteolytic enzyme activity continues unchecked and dissolves the fibrous tissue. This thin cap is susceptible to rupture, which exposes the thrombogenic interior arterial wall and produces a thrombus that extends into the arterial lumen. This lesion usually is labeled a *vulnerable plaque* because of the risk of rupture and life-threatening thrombosis. These lesions appear at about age 55 to 65 years, just before the peak incidences of myocardial infarction and stroke. See [Figure 1B](#) for an example.

Distribution of TCFA and ruptured plaques within coronary arteries is apparently highly focal and very limited in patients who are dying of cardiovascular causes. This contrasts with the extensive distribution in coronary arteries of all earlier grades of atherosclerotic lesions. Thin-cap atheroma and ruptured plaques, respectively, involved means of 1.6% and 1.2% of the epicardial portions of coronary arteries. Most of these lesions were limited to the proximal portions of the major coronary arteries, and 92% were clustered within ≤ 2 adjacent 20-mm artery segments.¹⁷ The plaque may grow into adjacent media and adventitia and distort them. As the plaque grows, the local segment of the arterial wall may enlarge its caliber, thus compensating for threatened reduction of the lumen by the plaque. This compensation, which is seen as remodeling, stops when the plaque occupies about 40% of the area of the artery. Any further plaque enlargement reduces the arterial lumen and may become hemodynamically significant. New vaso vasorum with thin walls invade the diseased intima from the media. These fragile vessels of endothelium, lacking pericytes for support, may leak, producing hemorrhage within the arterial wall. These intramural hemorrhages provoke increased fibrous tissue.

Complex Lesion Development

Many ruptures of thin fibrous caps (see above) are clinically silent in that they heal by forming fibrous tissue matrices of cells, collagen fibers, and extracellular space but may rupture again with thrombus formation.^{11–13} These cyclic changes of rupture, thrombosis, and healing may recur as many as 4 times at a single site in the arterial wall, resulting in multiple layers of healed tissue ([Figure 1C](#)). In 60% of sudden cardiac deaths, cyclic healing of clinically silent ruptures has been reported.¹³

Calcium deposits in the wall occur throughout all these steps, initially as small aggregates, and later as large nodules. Plaques may rupture into the lumen and expose the nodules, which become sites for thrombosis.

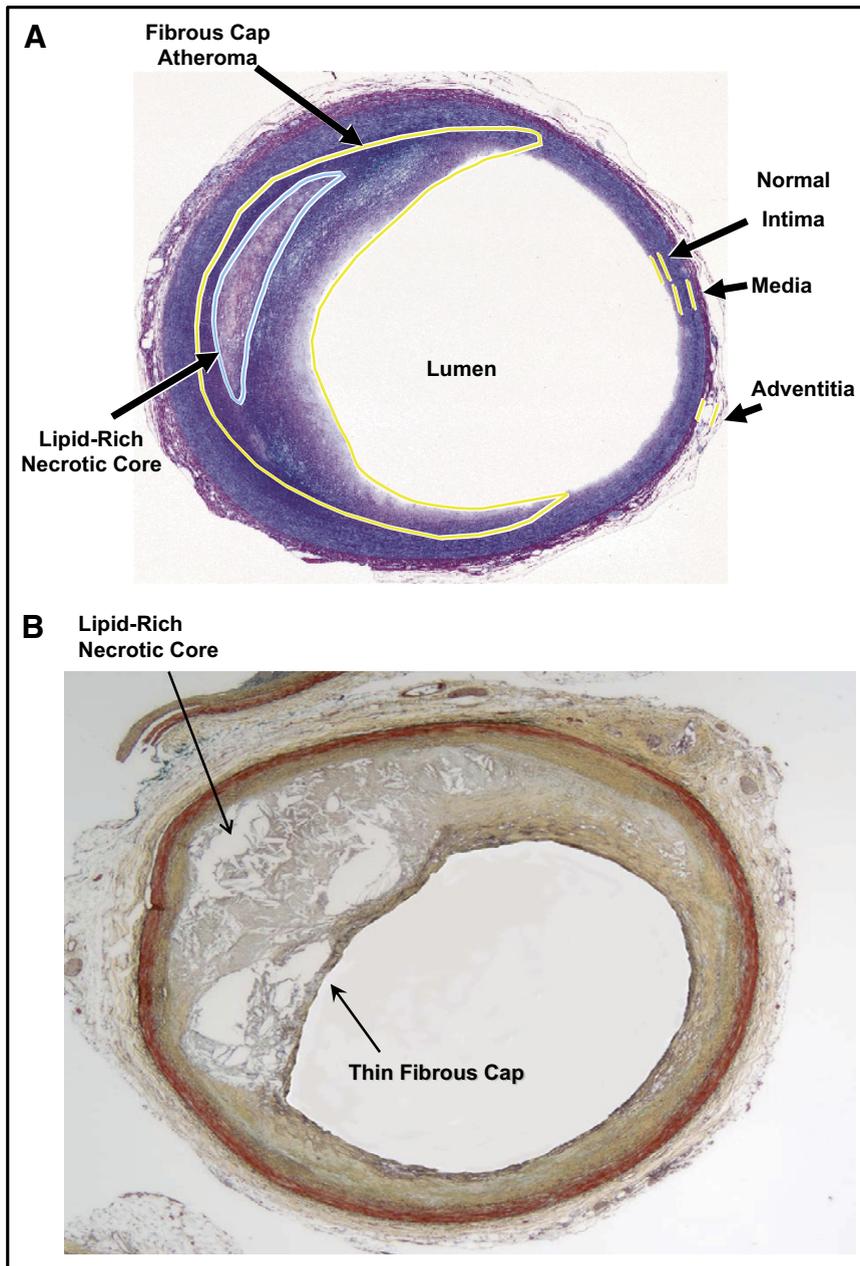


Figure 1 Histologic examples of 4 atherosclerotic plaque types. (A) Coronary fibrous cap atheroma in a 24-year-old man. (B) Thin fibrous cap atheroma.

Erosion of endothelium, underlain by some of the changes described previously or with no underlying histologic abnormality, may occur, resulting in thrombosis. The increasing mass of some plaques alone may become sufficient to form significant stenosis that may cause lethal ischemia simply through flow restriction (Figure 1D) (see also Figure 1 in the article by Ibañez and colleagues¹⁹ elsewhere in this supplement).

All of these changes may be significantly influenced by risk factors, notably the stresses of local hemodynamics and blood flow patterns, hypertension, tobacco smoking, and diabetes, as well as genetically determined arterial susceptibility or resistance to atherosclerosis. The mechanisms of these risk fac-

tors in influencing atherosclerosis are the target of intensive investigation by molecular pathology, along with proteomics and genomics, conducted to determine the exact molecular biological processes involved in their development.

UNDERSTANDING THE DEVELOPMENT OF ATHEROSCLEROSIS AS A SEQUENCE OF GROSSLY VISIBLE DIFFERENT ATHEROSCLEROTIC PLAQUES

Most of the histologic changes already described appear as gross plaques that are visible to the naked eye, but the fine

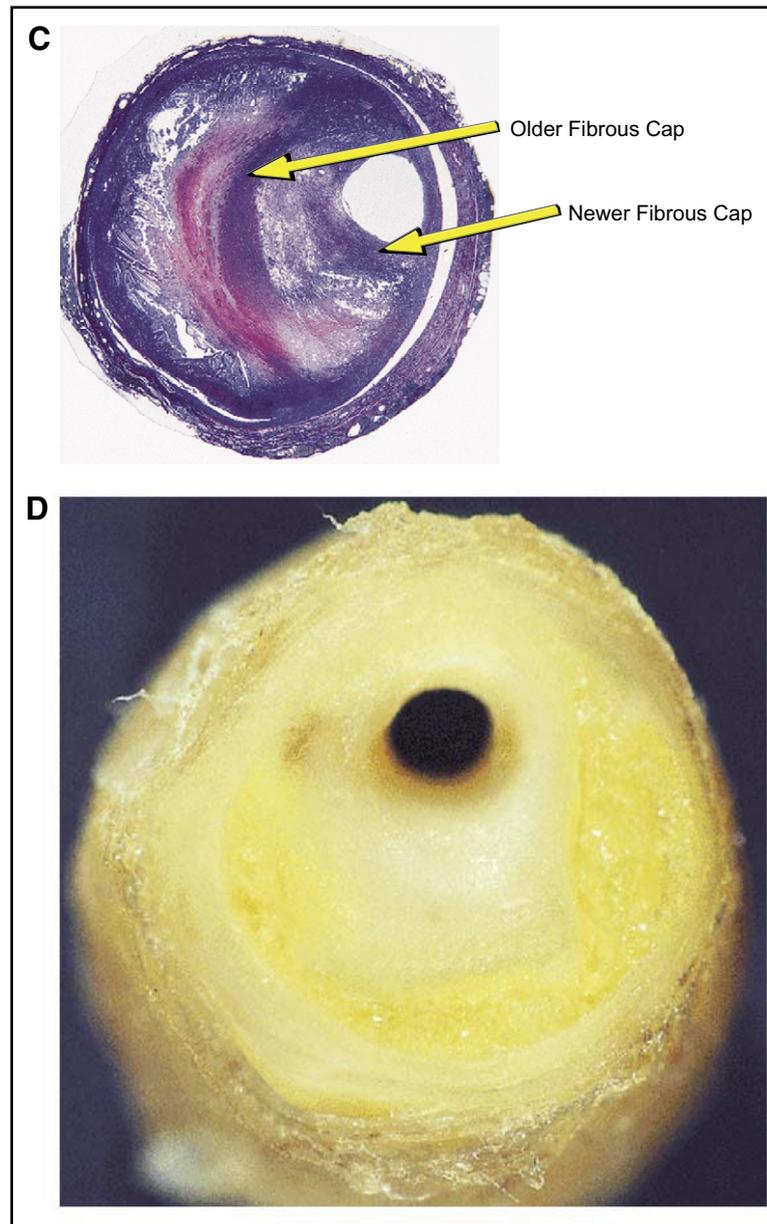


Figure 1 (Cont'd.) (C) Healed plaque rupture. (D) Stenosis of the anterior descending coronary artery in a 40-year-old man. (Reprinted with permission from *Atlas of Atherosclerosis: Progression and Regression*¹¹ and *Arterioscler Thromb Vasc Biol.*¹²)

histologic changes cannot be distinguished. For convenience and simplicity, it is useful to condense lesion development into classes of plaques that are grossly visible. Within the later portions of the developmental continuum are a series of advanced plaques that have been identified by differences in their gross appearance and histopathology that distinguish them from each other and from earlier and later changes. These major classes of plaques emphasize the advanced-stage plaques responsible for clinical disease and are summarized in Table 2.^{11,12,20} Four examples of these classes are shown in Figure 1.¹¹⁻¹³

Similar Types of Plaques Are Seen in Low-Risk and High-Risk Groups

Over the 40 to 50 years that atherosclerosis develops, time sequences for the continuously progressive development of grossly visible fatty streaks and fibrous plaques follow a pattern that is closely similar in all population groups over a range of risks for atherosclerotic cardiovascular disease.¹ For example, Figure 2 compares plaque development in white males with higher and lower risks, respectively, from New Orleans, Louisiana, and Santiago, Chile. Mortality rates for heart disease at ages 55 to 64 years, respectively,

Table 2 Major types of lesions of atherosclerosis

Lesion Name	Lesion Description by Histopathology	Thrombosis
Nonatherosclerotic intimal lesions		
1. Intimal thickening	The normal accumulation of SMCs in the intima with the absence of lipid or macrophage foam cells	Thrombus is absent
2. Intimal xanthoma or fatty streaks	Subendothelial accumulation of foam cells in intima without necrotic core or fibrous cap; animal and human data show that such lesions usually regress	Thrombus is absent
Progressive atherosclerotic lesions		
1a. Pathologic intimal thickening	SMCs in a proteoglycan-rich matrix with areas of extracellular lipid accumulation without necrosis	Thrombus is absent
1b. With erosion	Luminal thrombosis, plaque same as above	Thrombus most often mural and infrequently occlusive
2a. Fibrous cap atheroma	Well-formed necrotic core with overlying fibrous cap	Thrombus is absent
2b. With erosion	Luminal thrombosis; plaque same as above, no communication of thrombus with necrotic core	Thrombus most often mural and infrequently occlusive
3. TCFA	A thin fibrous cap infiltrated with macrophages and lymphocytes, rare SMCs, and an underlying necrotic core	Absent, with intraplaque hemorrhage/fibrin
a. With rupture	Fibroatheroma with cap disruption; luminal thrombus communicates with underlying necrotic core	Thrombus usually occlusive
4. Calcified nodule	Eruptive nodular calcification with underlying fibrocalcific plaque	Thrombus usually nonocclusive
5. Fibrocalcific plaque	Collagen-rich plaque usually with significant stenosis; contains large areas of calcification with few inflammatory cells; necrotic core may be present	Thrombus is absent

SMC = smooth muscle cell; TCFA = thin-cap fibroatheroma. Reprinted with permission from *Arterioscler Thromb Vasc Biol*.¹²

were reported as 878 deaths per 100,000 in a North American city comparable to New Orleans and 370 deaths per 100,000 in Santiago.²¹ In both groups, fatty streaks occur first at about 11 to 12 years of age; these are followed by fibrous plaques, starting at about age 15 to 30 years, depending on the individual's risk for atherosclerotic disease.¹⁶

Fibrous Plaques Develop More Rapidly in High-Risk Groups

Initially, both high-risk and low-risk groups develop fatty streaks, but shortly after the start of development, fibrous plaques become dominant and progressively expand to cover about 20% to 46% of the coronary arterial surface. Together, these plaques can reach a total extent of about 20% to 60% by age 60 years. In a comparison of males in high- and low-risk groups, fatty streaks were first noted at about the same ages (11 to 12 years), and similar growth rates of about 0.3% of surface per year were reported; however, in the high-risk group compared with the low-risk group, fibrous plaques tended to start at a younger age (17 years vs 23 years) and to grow more rapidly (0.8% vs 0.5% of surface per year).¹⁶

Plaque Development in Women Is Similar to That in Men

When women were compared with men at each geographic location (i.e., New Orleans and Santiago), closely similar

patterns of development and growth of fatty streaks and fibrous plaques were shown.¹⁶ Fibrous plaques appeared at the same anatomic sites as fatty streaks, indicating that fibrous plaques developed from fatty streaks.

Figure 2 is an example of data from the large International Atherosclerosis Project.^{1,22} However, detailed histologic information about the time course of fibrous plaque development between the ages of 35 and 55 years is not known. Patterns of plaque development as related to risk are a characteristic of atherosclerosis, having been observed in both sexes at 15 geographic locations, in 4 ethnic groups, and on 5 continents.¹⁶

It is important for the clinician to be aware that through a convention of pathology, individual plaques frequently are classified according to their most advanced stage of development, although earlier stages usually are present and are developing within zones adjacent to the plaque and in separate neighboring plaques.^{17,23–25} New plaques can be initiated at any time. This convention of staging and classification is clinically useful for individual patients because it emphasizes their kind of plaque, which determines their immediate risk for acute thrombosis or lethal ischemia.

SEQUENCE OF DEVELOPMENT OF HISTOLOGIC CLASSES OF PLAQUES THAT CAUSE SUDDEN CARDIAC DEATH

Hypothetical sequences of plaque development can be reasonably proposed because pathology studies now have out-

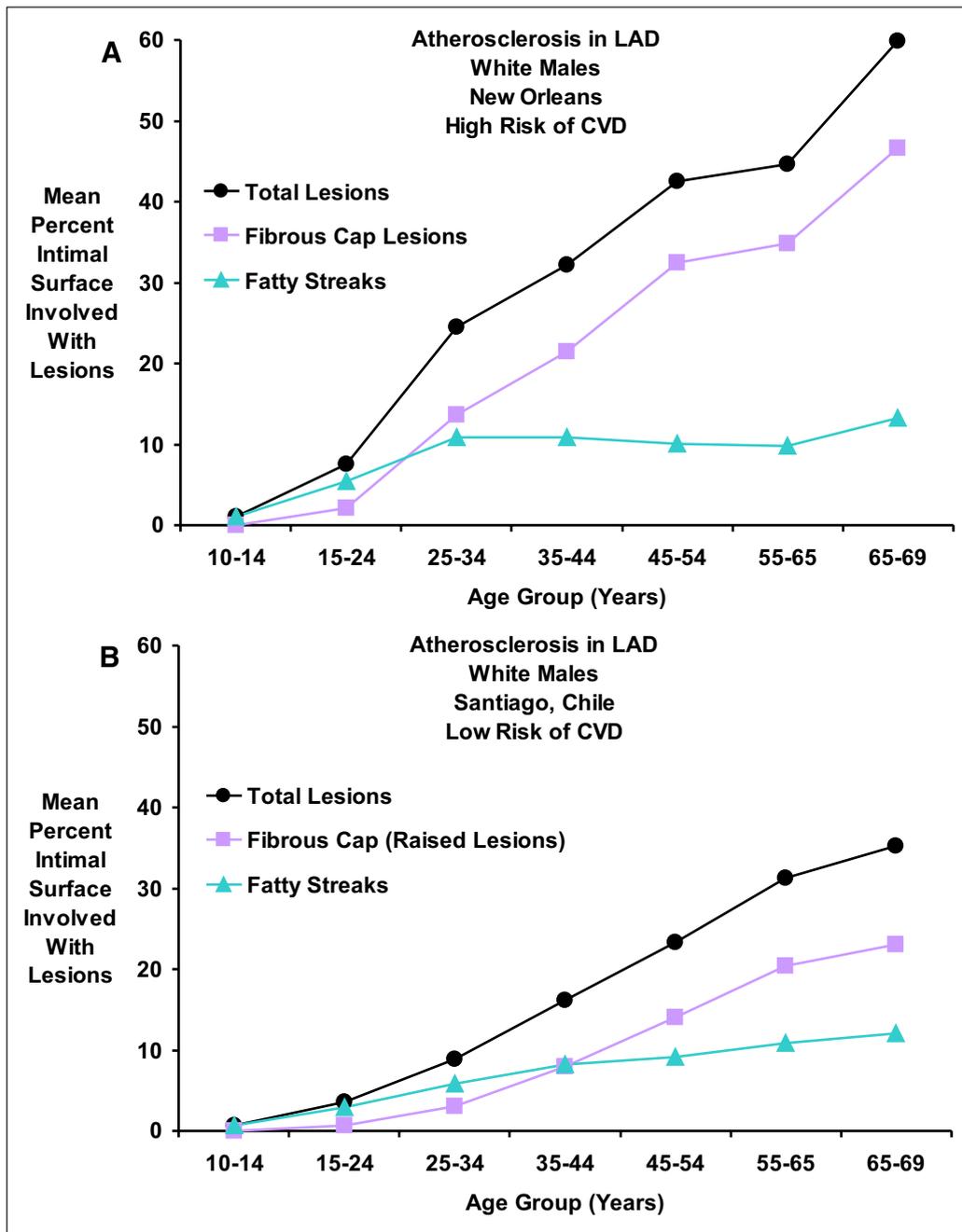


Figure 2 Increasing extent of atherosclerotic plaques with age. CVD = cardiovascular disease; LAD = left anterior descending. (Adapted with permission from *Lab Invest.*¹)

lined the complete sequence of development of major plaques from pathologic intimal thickening to fatty streaks, through fibrous cap atheromas, to plaques associated with sudden cardiac death.^{2,12,20} The hypothetical developmental sequences in Figure 3 are based on identification of precursor plaques for the 4 classes of sudden death by the logical criterion that they possess closely similar histopathologies.¹² For the clinical practitioner who is managing the individual patient, this sequence can serve as a useful guide to the choice of plaque imaging method, the plaque diagnosis, the plaque prognosis, and the choice of therapy.

Four major classes of plaques are associated with the acute coronary syndromes and sudden cardiac death (Figure 3).¹² Three classes of plaque are known to cause terminal events due to thrombosis, with the observed relative proportions of their prevalence as follows: thrombosis due to rupture of TCFA, ~50% to 60%; thrombosis due to erosion of the endothelium, ~20%; and thrombosis due to protrusion of a calcified nodule into the arterial lumen, ~2%. In the fourth class, fibrocalcific plaques, there is an advanced stenosis in the absence of thrombosis, with a prevalence of ~20% to 30%. This advanced stenosis is presumably suf-

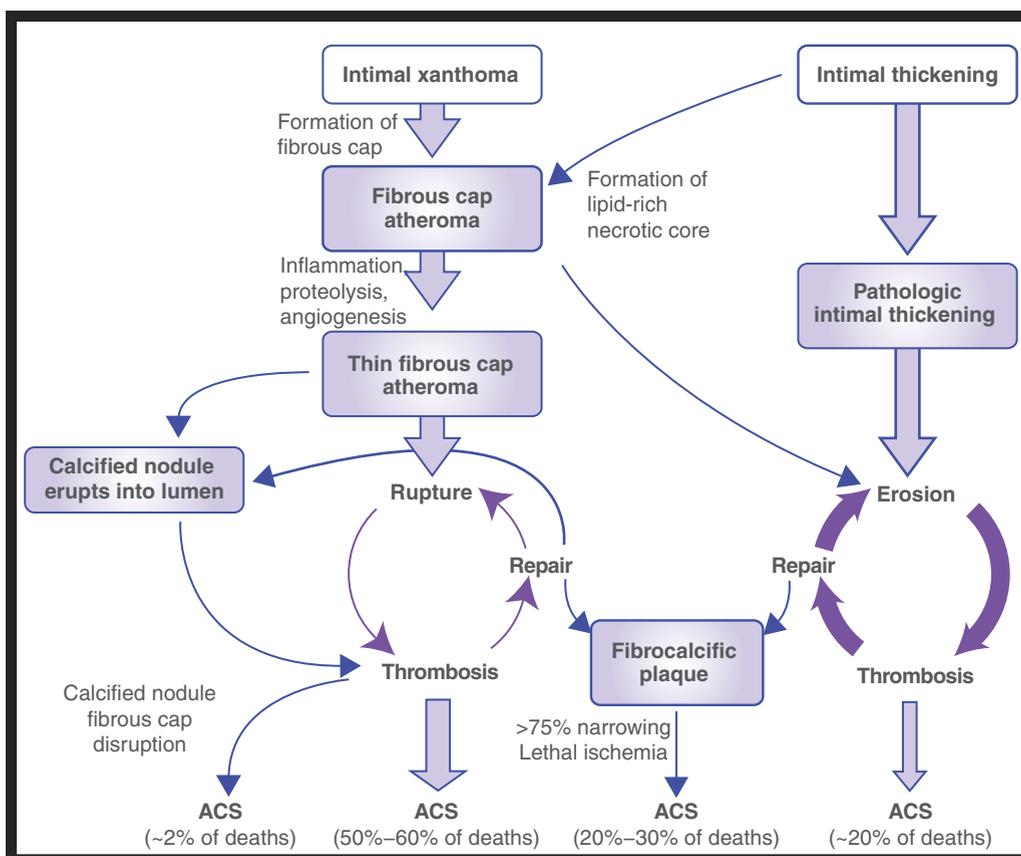


Figure 3 Flow chart of the general concepts of the development of atherosclerosis. ACS = acute coronary syndromes. (Adapted with permission from *Arterioscler Thromb Vasc Biol*.¹²)

ficient to provoke myocardial ischemia and fatal arrhythmia. Multiple cycles of subclinical plaque rupture or erosion, followed by thrombosis and healing, occur in 60% of sudden cardiac deaths before the fatal event. The histology of all these classes of lesions shows that subclinical coronary artery thrombosis had repeatedly occurred and healed up to 4 times (Figure 1C and Figure 3).^{12,13}

TREATMENT OF ATHEROSCLEROSIS CHANGES CLINICAL COURSE AND PLAQUE SIZE, COMPOSITION, AND BIOLOGICAL ACTIVITIES

Lipid treatments available to all practitioners have favorably changed atherosclerosis in terms of 5 fundamental measures: (1) risk of clinical events, (2) plaque size, (3) cellular composition, (4) plaque chemical composition, and (5) plaque biological activities centered on inflammation and cholesterol metabolism. These broad therapeutic effects have been demonstrated in numerous clinical trials undertaken to measure clinical events, in recent studies of arterial pathology, and, indirectly, in studies that measured changes in images of arteries and plaques. Clearly, all aspects of advanced stages of atherosclerosis can be favorably changed by current lipid treatments (Figure 4). Atherosclerosis should no longer be considered inexorably progressive, but can now

be regarded as partially controllable by treatment. Treatment effects on clinical pathology and on arterial pathology are reviewed below (see also articles by Bays²⁶ and Lewis²⁷ elsewhere in this supplement).

Clinical Course

When any lesion of the body, including an atherosclerotic plaque, is treated, the usual goal of treatment is to make it disappear or regress. However, a more pragmatic definition, appropriate to our current limited knowledge, is the following: "Regression of atherosclerosis refers to any change in an established atherosclerotic lesion that is favorable because it improves the [clinical] course of the disease."¹¹ The risks of clinical manifestations of atherosclerosis can be reduced by 20% to 40% with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) treatment. Controlled clinical trials of statins have demonstrated reduction in atherosclerotic cardiovascular morbidity and mortality, including angina pectoris, nonfatal and fatal myocardial infarction, uses of coronary bypass surgery and coronary artery angioplasty and stenting, transient ischemic attacks, stroke, and total mortality.^{28–31} The relative risk reductions are proportional to the magnitude of LDL cholesterol reduction over a broad range of absolute levels of LDL cholesterol. These data strongly indicate that statin treatment

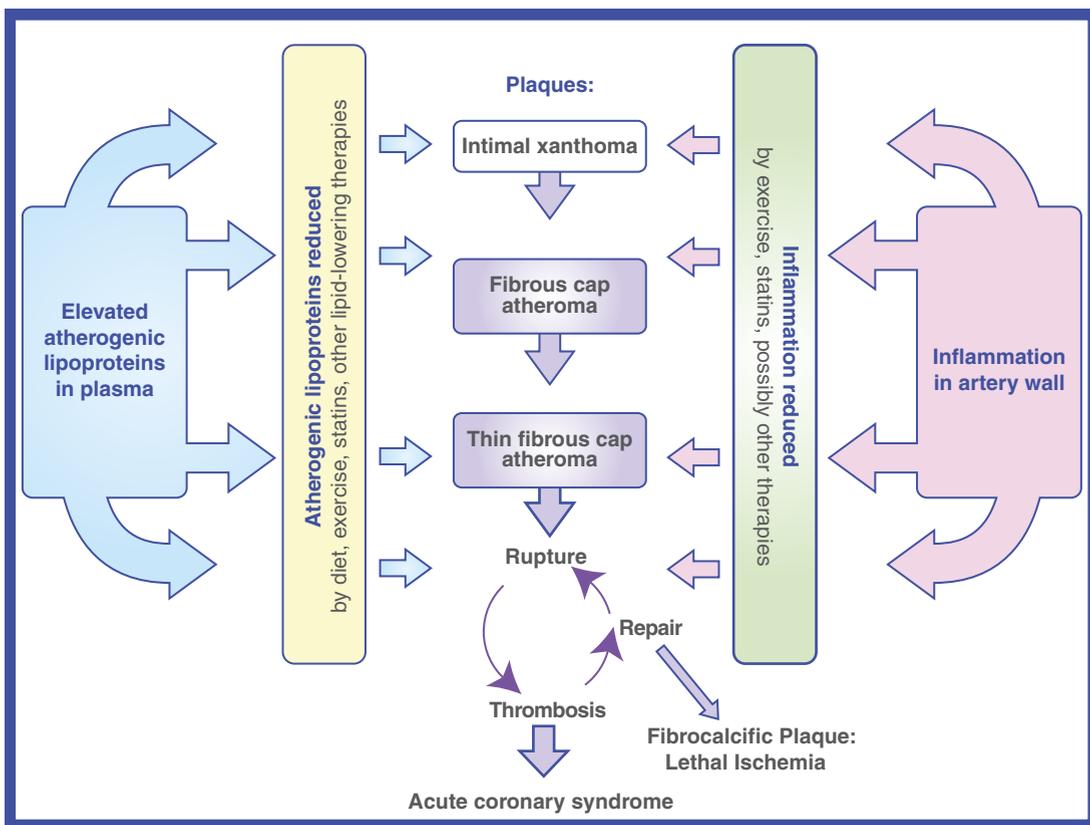


Figure 4 Influence of therapeutic intervention on the atherosclerotic process.

retards the development of atherosclerotic plaques and causes their stabilization.

Plaque Size

Treatment-induced changes in plaques have been demonstrated in clinical trials that directly measured images of plaques or parts of plaques. In these studies, statin treatment reduced the rate of plaque development and reduced plaque size. These trials have examined treatment effects across different patient populations using a variety of vascular imaging methods to measure carotid artery intima-media thickness (CIMT), carotid and aortic wall thickness, and coronary artery plaque volume.^{32–36} Statin treatments given for 18 to 24 months produced reduction of coronary plaque progression that was proportional to the new levels of LDL cholesterol.³⁷ Reduction of percent atheroma volume by $\geq 0.4\%$ occurred when LDL cholesterol was reduced to less than the mean of 87.5 mg/dL (1 mg/dL = 0.02586 mmol/L) and high-density lipoprotein cholesterol was increased by more than the mean of 7.5%.³⁷ Magnetic resonance imaging (MRI) studies of the effects of statin treatment on carotid atherosclerosis have shown slowing of progression,³⁸ stabilization,³⁴ or volumetric reduction.³³ Treatment with niacin plus colestipol reduced CIMT over 2 years.³⁹ Reduction in size of the lipid-rich necrotic core of advanced lesions occurred when LDL cholesterol was substantially lowered by statin treatment and plaques were measured by MRI.³⁴ It

appears that substantial reduction of LDL cholesterol is required to reduce plaque volume.

Plaque Composition and Biological Activities

The histology of advanced plaques has been changed substantially by short-term statin treatment, which alters the cellular composition, chemical composition, and biological activities of plaque. Recently, 4 trials of statin treatment directly measured the tissue components of advanced atherosclerotic plaque.⁴⁰ Tissues from carotid endarterectomy were analyzed by quantitative immunohistochemical techniques. Statin treatments, which reduced serum LDL cholesterol to an average of 90 mg/dL (range, 74 to 124 mg/dL) for 3 to 4 months, caused significant favorable alterations in the composition of advanced plaques. On average, statins reduced the plaque contents of macrophages by 57% and those of lymphocytes by 67%. The content of smooth muscle cells appeared to be sustained. Statins reduced the total lipid content by 72%, and collagen content increased by 160%. Biological activities associated with inflammation and oxidation were markedly decreased. Enzymes that lyse fibrous cap collagen and cause cap thinning and increased vulnerability to plaque rupture were reduced—matrix metalloproteinase (MMP)-2 content by 68% and MMP-9 content by 73%. Content of cyclooxygenase (COX)-2 enzymes responsible for oxidation was reduced. Changes in lesions induced by treatment meet many of the criteria suggested

for the occurrence of plaque stabilization.⁴¹ These statin-induced changes caused major disruptions in the usual atherogenic complex of abnormal lipid metabolism and inflammation in advanced plaques.

Additional studies are needed to enhance our understanding of the full extent and significance of these changes; investigators should seek to (1) identify the relation between drug doses and plaque responses, (2) determine the time courses of various responses of plaques during long-term therapy, (3) identify statin regimens to be used for optimal plaque treatment, (4) describe the nature of residual arterial abnormalities after statin treatment, and (5) select and test nonstatin treatments that target poststatin residual lesions and poststatin residual risks for clinical disease.

ATHEROSCLEROSIS TREATMENT: TIME TO BENEFIT AND DURABILITY OF RISK REDUCTION INDUCED BY LIPID THERAPIES

The time to clinical benefit from statin treatment appears to be as short as a few months. In patients receiving intensive statin treatment after acute coronary syndromes, a reduction in risk for clinical events occurred after 4 to 6 months in 2 trials, and after 1 month in a post hoc analysis from 1 of those trials.^{42–45} This indicates that extensive statin-induced changes in plaque tissue after 3 to 4 months of treatment probably have clinical benefits. Rigorous confirmation of this relation is not likely because few clinical trials will compare plaque changes in terms of histopathology versus clinical benefit. Instead, proof probably will be obtained through clinical trials undertaken to compare treatment-induced changes in plaque images versus changes in clinical events.

Statin treatment has durable effects in 2 ways. First, during statin treatment, cardiovascular risk benefits are sustained and cumulative. All long-term clinical trials of statins show sustained and increasing benefit compared with parallel treatment groups given placebo or a less effective comparator drug. Second, the durability of benefit of statin treatment after treatment has stopped is likely to be significant. In the West of Scotland Coronary Prevention Study (WOSCOPS), which tested the effects of pravastatin for 5 years, a substantial reduction in risk persisted 10 years after the study was terminated.⁴⁶ Another trial, which explored the use of niacin, has also shown durability of benefit. In the Coronary Drug Project, the reduction in cardiovascular risk induced by niacin treatment for 5 years resulted in an 11% reduction in mortality after 9 years without further lipid treatment.⁴⁷ These results indicate that with lipid treatment, acute clinical benefits “on treatment” were cumulative, and these benefits when “off treatment” were sustained persistently. Apparently, the usual trajectory of the progressive development of atherosclerotic plaque was slowed, and clinical events were delayed. A compensatory acceleration in development did not occur when patients were off treatment; benefits to the arterial walls were “put in the bank.”⁴⁸ Additional studies are needed to confirm and extend these

findings on the durability of treatment effects and to identify the mechanisms responsible for posttreatment outcomes.

ATHEROSCLEROSIS TREATMENT: THE FUTURE

The comprehensive effects of statins on plaque with partial control of atherosclerosis indicate that treatment with new drug regimens will be successful and will significantly change the course and risk of clinical events due to atherosclerosis. Future benefits may be >70% compared with the present usual maximum of ~40%. The study findings reported here can assist the clinician in selecting targets for future therapies designed to control remaining poststatin abnormalities in arterial tissues and plaques while reducing the residual risks of clinical disease.

SUMMARY

Recent clinical trial data on the pathology of advanced-stage arterial lesions of atherosclerosis demonstrate that statin treatment can begin to alter plaque composition and reduce plaque size within 1 to 4 months, resulting simultaneously in parallel reduction in the risk for clinical cardiovascular disease. Thus, atherosclerosis, a disease heretofore viewed as inevitably progressive, can be significantly treated to alter the arterial lesions and reduce their clinical consequences, thus fulfilling Stary’s pragmatic definition of plaque regression. These benefits can be attained by practicing clinicians who use approved drugs in combination with appropriate diet, exercise, weight control, and smoking cessation measures.

PEARLS FOR CLINICAL GUIDANCE

- Atherosclerosis develops over 50 years, from early teenage years to death.
- Atherosclerotic plaques develop as accumulations of cholesterol-rich lipids that incite inflammatory responses.
- Atherosclerosis affects all major conduit arteries, largely in their proximal portions.
- A small proportion of the most advanced plaques in the coronary arteries or the cerebrovascular arteries can cause sudden death due to thrombotic occlusion or ischemic stenosis.
- Each person’s extent of atherosclerosis depends on his or her risk factors and arterial susceptibility.
- Lipid treatment can produce favorable major changes in the composition of advanced plaques within 4 months, resulting in clinical benefit.
- Clinical benefit that continues after lipid treatment for atherosclerosis has ceased may be fully durable for at least 10 years, indicating the durability of histologic alterations of the artery.

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William Insull, Jr., MD, serves on the Speakers' Bureau for Abbott Laboratories, Merck & Co., Inc., and Schering-Plough Corporation and as a consultant/advisory board participant for Daiichi Sankyo, Inc., Merck & Co., Inc., and Merck/Schering-Plough, Inc. He is an investigator for Pfizer Inc and has received research support from AstraZeneca Pharmaceuticals LP, Kos Pharmaceuticals, Inc., Merck & Co., Inc., and Pfizer Inc. In addition, Dr. Insull has received honoraria from Merck & Co., Inc., and from Merck/Schering-Plough, Inc., and is an editor/writer for AstraZeneca Pharmaceuticals LP.

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