Atherosclerosis

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Cell Biology, and Physiology
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- Overview of atherosclerosis and atherothrombotic vascular disease
- Theories of atherogenesis and advanced lesion progression
- The macrophage foam cell
- Clinical implications
Of all the ailments that might blow out life's little candle, heart disease is the chief.

William Boyd (1885-1972)
Pathology for the Surgeon

Coronary Arteries
Unoccluded Coronary Artery

Occluded Coronary Artery

Thrombus

Necrotic atherosclerotic lesion
Progression of Atherothrombotic Vascular Events

Abrams (2005) NEJM 352:2524
Atherosclerosis

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Atherogenesis
Subendothelial Lipoprotein Aggregation and Matrix-Retention

Tabas et al., Circulation, 2007
Maladaptive Responses to Lipoprotein Retention are Key Processes in Lesion Progression... But They Can't Explain Lesion Initiation
Don't Forget the Root Cause!

Atherosclerosis: the role of endothelial injury, smooth muscle proliferation and platelet factors

Mechanisms of Disease

Franklin M. Epstein, M.D., Editors

Atherosclerosis — An Inflammatory Disease

Oxidation, lipoproteins, and atherosclerosis: which is wrong, the antioxidants or the theory?

Recent Discoveries and Novel Hypotheses
Regression: The "Orange Arrows"

Regression of Atherosclerosis
Acute Atherothrombosis
The Trigger for Acute Coronary Syndromes

The Plaque Rupture Theory of Acute Atherothrombosis
Plaque Morphology is More Important than Plaque Size
Mild-to-Moderate Lesions that Rupture are the Most Common Cause of Cardiac Events

Plaque Rupture

Ruptured plaque at area of thinned fibrous cap

Necrotic Core

Thrombus
The Problem

“Benign” atherosclerotic lesion ➔ Ruptured “vulnerable” plaque

Crawford et al. ATVB 1998; Constantinides

The Importance of Advanced Lesional Mφ Death

Necrotic Core “graveyard of dead Mφs”
The Importance of Advanced Lesional Mφ Death

Necrotic Core
“graveyard of dead Mφs”

inflammation
coagulation
thrombosis
proteases
stress on fibrous cap

Mφ Death in Advanced Atherosclerosis

Thrombus
Fibrous cap
Plaque rupture

ADVANCED LESION
Apoptotic advanced lesional macrophage (e.g. PC-loading, cryoprobos)
Defective phagocytic clearance

Necrotic core
Debris and inflammation
Secondary necrosis of macrophage

Tabas ATVB Nov 2005
Atherosclerosis

- Overview of atherosclerosis and atherothrombotic vascular disease
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  PICTURE GALLERY
- The macrophage foam cell
- Clinical implications

The Fatty Streak

Focal Accumulations of Cholesterol
"Foam Cells"
The Cellular Component of the Fatty Streak

Fibrous Lesion

Fibrous cap
SMCs

MΦs
Fibrous Lesion with Necrotic Core

Fibrous cap

Necrotic core

Necrotic Center
- Cell Debris
- Cholesterol Crystals
- Cholesteryl Esters
- Calcium

Endothelium

Fibrous Cap
- Proliferated Smooth Muscle Cells
- Collagen Extracellular and Intracellular Lipid
- Including Foam Cells

Media
Plaque Rupture

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The Macrophage Foam Cell

"Nature and Origin of the Xanthoma ('Foam') Cell"
L.W. Plewes (1934) Archiv. Pathol. 17:177-186

EM of atherosclerotic aortic intima from a patient given Thorotrast prior to death
"I believe that the origin of the [foam cell] is from the reticulo-endothelial system, and that the foam cell is an evidence of [a] specific reaction . . . to certain lipoids, especially cholesterol and its esters, when conditions favorable for their deposition in tissues are present."

Immunohistochemical Identification of Atherosclerotic Macrophage Foam Cells

expanded intima filled with "foam cells"

hematoxylin and eosin mAB to MΦ surface antigen
The Life Cycle of the Macrophage Foam Cell

**Monocyte Chemotaxis**

The Life Cycle of the Macrophage Foam Cell

**Diapedesis**
The Life Cycle of the Macrophage Foam Cell

Differentiation

The Life Cycle of the Macrophage Foam Cell

? Proliferation
The Life Cycle of the Macrophage Foam Cell
Continued Macrophage Recruitment

Lumen
Subendothelium

The Life Cycle of the Macrophage Foam Cell
Cholesteryl Ester Accumulation

Lumen
Subendothelium
Macrophage Foam Cell Formation

The Life Cycle of the Macrophage Foam Cell
Cholesterol Efflux
The Life Cycle of the Macrophage Foam Cell

Macrophage Egress

- lumen
- subendothelium
- ? dendritic cell

Apoptosis

- cholesterol, oxidized lipids, growth factor depletion
- apoptotic Mφ
The Life Cycle of the Macrophage Foam Cell

? Phagocytosis of Apoptotic Body

? Disposal of Apoptotic Body
The Life Cycle of the Macrophage Foam Cell
Mφ "Necrosis" or "Aponecrosis"

Lesional Necrosis: The Lipid (or Necrotic) Core

Mφ "Necrosis" or "Aponecrosis"
The Life Cycle of the Macrophage Foam Cell

Plaque Rupture

The Life Cycle of the Macrophage Foam Cell

Acute Thrombosis and Vascular Occlusion
Overview of atherosclerosis and atherothrombotic vascular disease

Theories of atherogenesis and advanced lesion progression

The macrophage foam cell

Clinical implications
Lowering Plasma LDL Decreases Coronary Artery Disease

Lowering Plasma LDL Decreases Coronary Artery Disease

Why?

Atherothrombotic vascular disease

Maladaptive inflammatory response

Diffuse intimal thickening (DIT) apoB-LPs in plasma Endothelium VSMCs in media Retained LPS Expanded intima, rich in retentive proteoglycans Monocyte T cell Dying Mφ Mφ foam cell Plaque necrotic with cholesterol crystals

Why?

Maladaptive inflammatory response

Pre-TEENS

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Why?

Maladaptive inflammatory response
Atherogenesis

"High" levels of apoB-lipoproteins in the bloodstream + A "susceptible" arterial wall (i.e., susceptible to apoB-LP retention or responses to retention)

Therapeutic Approach to Prevent and Reverse Atherosclerosis

"High" levels of ApoB-lipoproteins in the bloodstream

↓ Probability of ApoB-LP entry and then retention in the subendothelium
Don't Forget the Time Frame!

- 2-yr "risk"
  - Post-ACS studies
  - CIMT studies

- 10-yr risk
  - Framingham risk score

- Lifetime risk
  - Most meaningful metric for risk assessment of CAD, a disease that takes decades to develop

Clinical Predictions

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<th>Arterial Wall Susceptibility (genes; lifestyle)</th>
<th>Plasma LDL</th>
<th>Lifelong Risk of CAD</th>
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<td>Average</td>
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<td>Low</td>
<td>High</td>
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*low end of the bell-shaped curve for modern industrialized societies
Case Study
Mrs. M

- 64 y/o female with 20-yr hx of type 2 diabetes and HTN
- smokes one ppd cigarettes
- moderately obese
- Het FH: LDL = upper 200's; HDL = upper 30's; TG = low 300's
- on Rx for diabetes, hypertension, and dyslipidemia but is non-compliant
- refuses to stop smoking, engage in an exercise program, or lose weight
- no clinical hx of CAD, CVA, or PAD; EKG and stress test normal

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## Current ATP III Treatment Guidelines
### Last updated 2004

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- high Framingham risk
- symptomatic athero d.
- diabetes

*Post-hoc TNT & IDEAL: for subjects on statins, better predictor than LDL (Circ 2008)
## NCEP ATP III Treatment Guidelines

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<th>Therapeutic Lifestyle Change (TLC)</th>
<th>Pharmacologic Treatment</th>
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<tr>
<td>Improve diet</td>
<td>Statins (HMG-CoA reductase inhibitors)</td>
</tr>
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<td>Weight reduction</td>
<td>Fibrates</td>
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<tr>
<td>Physical activity</td>
<td>Niacin</td>
</tr>
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<td></td>
<td>Bile acid sequestrants</td>
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<tr>
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<td>Cholesterol absorption inhibitors</td>
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<td><strong>Combinations of the above</strong></td>
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## It Ain’t Happening

*Am Heart J. July 2008*: NHANES $\rightarrow$ only 37% of those with CVD were at target LDL goals in 2003-2004

*Circulation July 2008*: If goals were actually met, MI and strokes would be lowered by 63% and 31%, respectively, and 224 million quality-adjusted life-years would be added over the next 30 yrs
### Current ATP III Treatment Guidelines

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**Ongoing developments:**
- Lower is better
- Earlier is better

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*Circulation* 2008;118;672-677

### Evidence Mandating Earlier and More Aggressive Treatment of Hypercholesterolemia

Daniel Steinberg, MD, PhD; Christopher K. Glass, MD, PhD; Joseph L. Witzum, MD
Lower is Better
Cholesterol Levels Among Different Human Populations

![Graph showing cholesterol levels among different human populations.]

Mean total cholesterol, mg/dL

- Hazda
- Inuit
- !Kung
- Pygmy
- San
- Adult American


Lower is Better and "Safe"

- Hunter-gatherer societies (and other mammals)
- Cord blood
- Familial hypobetalipoproteinemia
- "Zero-risk" extrapolation of LDL-lowering trials
- PROVE-IT subgroup
- LDL receptor is 50% saturated at 10 mg/dl
The Great Debate of 2008—How Low to Go in Preventive Cardiology?

Eric D. Peterson, MD, MPH
Tracy L. Wang, MD, MS

The debates of 2008 have already been quite intense. During this election year, politicians and pundits alike, reviewing the same set of information, have formulated remarkably different conclusions and recommendations for national policy. The field of preventive cardiology has likewise been witness to its own debate spurred by a series of important yet somewhat unexpected clinical trial results, the question of “how low to go” in cardiovascular risk-factor modification has been hotly disputed.

The debate is not new and traditionally has been waged between the “true believers,” those with a strong a priori conviction that more aggressive pharmacological treatment will reduce future events, and the “therapeutic nihilists,” those who require unequivocal proof before acceptance. In recent years, the true believers have had the upper hand. Epidemiological data have consistently concluded that lower levels of lipids, blood pressure, and glucose all correlate with less cardiovascular disease. Similarly, among patients with established cardiovascular disease, intensive lipid lowering with statins has been demonstrated to reduce future cardiac events. Thus, national treatment guidelines have progressively lowered their thresholds for initiation of drug therapy as well as the target levels to be achieved. Yet the benefit of aggressive pharmacological therapy for primary prevention is less clear, even among high-risk subgroups. Additionally, while statin therapy appears beneficial for hypertensive patients, the ideal target for low-density lipoprotein cholesterol (LDL-C) or blood pressure lowering in these patients have not been defined. How low is the line? Where is the evidence that intensive lowering is necessarily better or even safe?

In this issue of JAMA, Howard and colleagues report the results of the Stop Atherosclerosis in Native Diabetics Study (SANDS), which compared aggressive therapy of systolic blood pressure and LDL-C lowering to standard therapy among American Indian patients with type 2 diabetes mellitus. This is one of the first studies to assess the role of aggressive risk factor modification in a high-risk primary prevention setting. The study was well-designed and rigorously conducted with patient follow-up every 3 months for up to 3 years. The authors also examined these questions in a tradition of underrepresented populations. The results showed that patients receiving intensive management had significant regression of carotid intimal medial

See also: p 1678.

1718 JAMA, April 9, 2008, 300:2, 1718-1720. [Reprinted]
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Earlier is Better

Regression is More Robust When Starting With Earlier Lesions

Earlier is Better

- Adolescents
- Life-long low risk by 50 y/o = very low future risk
- Best predictor of CAD = risk profile 15 yrs prior
- PCSK9
- Children with FH
- 2007 AHA/AAP guidelines
Is Long-Term Use of High-Dose Statins Completely Safe?
Of all the ailments that might blow out life's little candle, heart disease is the chief.

William Boyd (1885-1972)
*Pathology for the Surgeon*