Atherosclerosis

Ira Tabas, M.D., Ph.D.
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Cell Biology, and Physiology
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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-300'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
Atherosclerosis

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

- Epidemic of obesity
- Aging of the population

William Boyd (1885-1972)
Pathology for the Surgeon
Coronary Arteries

Aorta

Right atrium

Right ventricle

Pericardium
Unoccluded Coronary Artery
Occluded Coronary Artery

Thrombus

Necrotic atherosclerotic lesion
Progression of Atherothrombotic Vascular Events

Abrams (2005) NEJM 352:2524
Progression of Atherothrombotic Vascular Events

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Atherosclerosis

- Overview of atherosclerosis and atherothrombotic vascular disease
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- The macrophage foam cell
- Clinical implications
Diffuse intimal thickening (DIT) → apob-LPs in plasma → Endothelium → VSMCs in media → Retained LPSs

Cholesterol, fatty acids, oxidized proteins and lipids

Tabas et al., Circulation, 2007
Subendothelial Lipoprotein Aggregation and Matrix-Retention
Tabas et al., Circulation, 2007
Atherothrombotic vascular disease

Plaque necrosis with cholesterol crystals

Diffuse intimal thickening (DIT)  apoB-LPs in plasma  Endothelium

VSMCs in media

Retained LPs

Expanded intima, rich in retentive proteoglycans

Monocyte

Intima SMC

Mφ foam cell

Mφ

Fibrous cap

Mast cell

T cell

Dying Mφ

Tabas et al., Circulation, 2007
Causative Evidence in Support of the Response to Retention Model of Atherosclerosis

• No ApoB lipoproteins → no maladaptive inflammatory response and no atherosclerosis (animals and humans)—diet, genetic, or therapeutic

• Decrease retention → decrease atherosclerosis (mouse models that alter ApoB or proteoglycans or interfere with their interaction with each other)

• Failure of other theories to meet these criteria (failure of anti-oxidants or anti-inflammatory Rx)
Important Lessons From the Response to Retention Model of Atherosclerosis

• Don't forget the root cause

• Don't forget the time frame

• Interplay between plasma apoB-LPs and arterial wall "susceptibility"

• Concept of retention amplification in progression

• Regression is inversely proportional to lesion stage
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


Special Report
Atherosclerosis 2005

Recent Discoveries and Novel Hypotheses


Review

Beyond cholesterol – inflammatory cytokines, the key mediators in atherosclerosis

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

Current Opinion in Clinical Nutrition & Metabolic Care. 8(2):139-146
March 2005
Cholesterol Veers Off Script

Recent drug trials have produced surprising results; along with genetics research, these findings have put in question some long-held beliefs.

CHOLESTEROL NUMBERS ARE A MANTRA OF medicine, and millions of us regularly supply a vial of blood to measure this waxy substance that circulates in the bloodstream. All cells need it to survive. But it also feeds plaques in the arteries that can break open, causing a heart attack. Controlling cholesterol is gospel in cardiovascular medicine; it guides treatment and sells billions of dollars' worth of drugs. It has also been reinforced by a Hollywood-like story line: A villainous "bad" cholesterol clogs arteries, and a valiant "good" cholesterol clears them.

The cholesterol hypothesis "is like religion for some people," says Harlan Krumholz, a cardiologist at Yale University. "They've been taught it in medical school. They've been taught it forever."

But Krumholz and some others say that after many decades, the cholesterol story is turning out to be messier and more nuanced than previously believed. Scientists increasingly recognize that good and bad cholesterol, though often spoken of in the same breath, are not equally well-understood. Hundreds of studies have shown that an overabundance of bad cholesterol, known as LDL (low-density lipoprotein), is associated with heart attacks. Good cholesterol, or HDL (high-density lipoprotein), is thought to be protective, but evidence for HDL's benefit is flimsier. Some scientists are now asking whether HDL is even relevant to heart-disease risk at all. Other fundamental questions persist: Why do people with healthy cholesterol levels still suffer heart attacks? Does the mechanism by which drugs tackle cholesterol matter to health? "You ask 20 peo-
Acute Atherothrombosis
The Trigger for Acute Coronary Syndromes

Abrams (2005) NEJM 352:2524
The Plaque Rupture Theory of Acute Atherothrombosis

- Intima
- Endothelium
- Thin fibrous cap
- Diffuse intimal thickening (dense collagen, sparse smooth muscle cells)
- Thrombus
- Macrophages
- Cholesterol, old hemorrhage, cell debris, calcium
- Necrotic core
Plaque Morphology is More Important than Plaque Size
Mild-to-Moderate Lesions that Rupture are the Most Common Cause of Cardiac Events

Thin fibrous cap
Necrotic core
Inflammatory milieu
Plaque Rupture

Ruptured plaque at area of thinned fibrous cap

Thrombus

Necrotic Core
The Problem

"Benign" atherosclerotic lesion

Ruptured "vulnerable" plaque

Crawford et al. ATVB 1998; Constantinides
The Necrotic Core

Necrotic Core
"graveyard of dead Mφs"
The Vulnerable Plaque

Necrotic Core
"graveyard of dead Mψs"

- inflammation
- coagulation thrombosis
- proteases
- stress on fibrous cap
The Vulnerable Plaque

Living Mφs

Necrotic Core
"graveyard of dead Mφs"

inflammation
coagulation thrombosis
proteases
stress on fibrous cap
The Vulnerable Plaque

- Necrotic Core: "graveyard of dead Mφs"
  - inflammation
  - coagulation thrombosis
  - proteases
  - stress on fibrous cap

- Dead SMCs
- Living Mφs
- \( \downarrow \) collagen
Atherosclerosis

- Overview of atherosclerosis and atherothrombotic vascular disease
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- 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
Fibrous Lesion with 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
Atherosclerosis

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Immunohistochemical Identification of Atherosclerotic Macrophage Foam Cells

hematoxylin and eosin

mAB to Mφ surface antigen

expanded intima filled with "foam cells"
The Life Cycle of the Macrophage Foam Cell

Monocyte Chemotaxis

- chemokines
- adhesion molecule
- matrix-retained and modified lipoproteins

subendothelium
The Life Cycle of the Macrophage Foam Cell

Differentiation

lumen

subendothelium
The Life Cycle of the Macrophage Foam Cell

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

Cholesteryl Ester Accumulation
Macrophage Foam Cell Formation

- Lumen
- Monocyte
- Endothelial cell
- Foam cell
- CE droplets
The Life Cycle of the Macrophage Foam Cell

Cholesterol Efflux

lumen

subendothelium

HDL

ApoA1/E
The Life Cycle of the Macrophage Foam Cell

? Macrophage Egress

lumen

subendothelium

? dendritic cell

lymphatics
The Life Cycle of the Macrophage Foam Cell

Apoptosis

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

? Phagocytosis of Apoptotic Body

lumen

subendothelium
The Life Cycle of the Macrophage Foam Cell

? Disposal of Apoptotic Body
The Life Cycle of the Macrophage Foam Cell

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

Lesional Necrosis: The Lipid (or Necrotic) Core
The Life Cycle of the Macrophage Foam Cell

Plaque Rupture

lumen

subendothelium

Mφ debris
The Life Cycle of the Macrophage Foam Cell
Acute Thrombosis and Vascular Occlusion
Mφ Death in Atherosclerosis

Lumen

EARLY LESION

TNFα
MMPs
IL1β

Macrophage foam cell

Apoptosis of macrophage foam cell

Phagocytosis of apoptotic body

Modulation of early lesion cellularity
Mφ Death in Atherosclerosis

**EARLY LESION**
- TNFα
- MMPs
- IL1β

**ADVANCED LESION**
- Apoptotic advanced lesion macrophage (e.g., FC-loading, oxysterols)
- Defective phagocytic clearance
- Secondary necrosis of macrophage

**Modulation of early lesion cellularity**
- Phagocytosis of apoptotic body
- Apoptosis of macrophage foam cell

**Thrombus**
- Lumen
- Fibrous cap
- Plaque rupture
- Necrotic core
- Debris and inflammation
Mφ Death in Atherosclerosis

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**Plaque rupture**

**Thrombus**

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Lowering Plasma LDL Decreases Coronary Artery Disease

Lowering Plasma LDL Decreases Coronary Artery Disease

Why?

% with CAD event vs. LDL-C (mg/dL)

Primary prevention trials: HPS, AFCAPS, CARE

Secondary prevention trials: WOSCOPS, LIPID, 4S, SCOPS
Maladaptive inflammatory response

Atherothrombotic vascular disease

Diffuse intimal thickening (DIT) apob-LPs in plasma Endothelium

VSMCs in media

Retained LPs

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Plaque necrosis with cholesterol crystals

Maladaptive inflammatory response

Dying Mφ

T cell
Atherogenesis

"High" levels of apoB-lipoproteins in the bloodstream

+ 

A "susceptible" arterial wall

(i.e., susceptible to apoB-LP retention or responses to retention)
"Susceptibiloscope"

- Family history

- Other arterial-wall risk factors: low HDL, diabetes/obesity, smoking

- Imaging & "biomarkers" (calcium score, HR CT, CRP): not very useful yet

- Future: personalized gene chip
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 Get Fooled!

Cholesterol Veers Off Script

Recent drug trials have produced surprising results; along with genetics research, these findings have put in question some long-held beliefs.

CHOLESTEROL NUMBERS ARE A MANTRA OF medicine, and millions of us regularly supply a vial of blood to measure this waxy substance that circulates in the bloodstream. All cells need it to survive. But it also feeds plaques in the arteries that can break open, causing a heart attack. Controlling cholesterol is gospel in cardiovascular medicine; it guides treatment and sells billions of dollars' worth of drugs. It has also been reinforced by a Hollywood-like story line: A villainous “bad” cholesterol clogs arteries, and a valiant “good” cholesterol clears them.

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At the same time, new genetic studies are yielding disparate results that undermine assumptions about cholesterol. This has left scientists puzzled, with some considering whether an altogether different risk factor, inflammation, is a missing link. Next month, a study of a cholesterol-lowering drug that may also reduce inflammation will report a benefit for the heart.

The bad actor
Cholesterol was first tied to heart disease in 1910, when a German chemist found that people with atherosclerosis had a high concentration of cholesterol in their aortas. Feeding rabbits cholesterol dissolved in sunflower oil caused severe atherosclerosis, cementing the connection.

A fatty substance that’s both made by the body and ingested in food, cholesterol helps build cell membranes and form hormones, as well as performing many other tasks. It doesn’t dissolve in the blood but instead is carried from place to place by bulky complexes called lipoproteins. Two of these travel opposite routes: LDL transports cholesterol from the liver to other tissues, and HDL is thought to carry it from other tissues, such as the arteries, back to the liver.
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

<table>
<thead>
<tr>
<th>Arterial Wall Susceptibility (genes; lifestyle)</th>
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*low end of the bell-shaped curve for modern industrialized societies
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*low end of the bell-shaped curve for modern industrialized societies*
# NCEP ATP III Treatment Guidelines

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

*Am Heart J.* July 2008: NHANES → 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

Last updated 2004

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dL)</th>
<th>Non-HDL-C Goal (mg/dL)</th>
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<tbody>
<tr>
<td>≤1 RF</td>
<td>&lt;160</td>
<td>&lt;190</td>
</tr>
<tr>
<td>≥2 RFs</td>
<td>&lt;130-100</td>
<td>&lt;160-130</td>
</tr>
<tr>
<td>CAD or CAD risk equivalent</td>
<td>&lt;100-70</td>
<td>&lt;130-100</td>
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- high Framingham risk
- symptomatic athero d.
- diabetes

**Ongoing developments:**
- Lower is better
- Earlier is better
Evidence Mandating Earlier and More Aggressive Treatment of Hypercholesterolemia

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

Mean total cholesterol, mg/dL

Hazda
Inuit
!Kung
Pygmy
San
Adult American

50 70 90 110 130 150 170 190 210

Hunter-gatherer humans

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 Y. 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.

This 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. Epidemiologic 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 targets for low-density lipoprotein cholesterol (LDL-C) or blood pressure lowering in these patients have not been defined. Here lies the doubt of the nihilists: “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 traditionally understudied population. The results showed that patients receiving intensive management had significant regression of carotid intimal medial

See also p 1678.
Earlier is Better


<table>
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<tr>
<th>Age, Decades</th>
<th>Subjects %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
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- fatty streaks
- fibrous plaques
- advanced lesions
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
Storm over Statins — The Controversy Surrounding Pharmacologic Treatment of Children
Sarah de Ferranti, M.D., M.P.H., and David S. Ludwig, M.D., Ph.D.
Take Home Messages

• Don't forget the root cause
• Don't forget the time frame
• Interplay between plasma apoB-LPs and arterial wall "susceptibility"
• Concept of retention amplification in progression
• Regression is inversely proportional to lesion stage