Atherosclerosis, Lipids and Lipoproteins
Objectives

• Describe the functions and sources of cholesterol and triglycerides
• Describe the functions and role of lipoproteins in atherosclerosis
• Explain the pathogenesis of atherosclerosis
• Identify the role of inflammation in atherosclerotic process
Presentation Outline

• Pathophysiology of Atherosclerosis
  – Early, Middle and Late Stages
  – Interaction among key elements: endothelial dysfunction, lipoprotein B particle infiltration and oxidation, inflammation, plaque rupture, thrombosis

• Lipid and Lipoprotein Metabolism
  – Key principles
  – Key lipoproteins
  – Key enzymes and transfer proteins

• Common Atherogenic Dyslipidemias
  – Elevated LDL & related (↑LDL-C, non-HDL-C, apo B, LDL-P)
  – Elevated TG, low HDL, small, dense LDL
  – Elevated Lp(a)
  – Mixed dyslipidemias
ATHEROGENESIS OVERVIEW
Atherosclerosis:
A *single* pathologic process beginning early in life, potentially in utero that progresses throughout the lifetime and is the *greatest* cause of death and disability in the Western world (~1/3 of all US mortality)
Atherogenesis Overview

Most atherosclerosis/CVD risk factors are lipoproteins or are lipoprotein-related
Atherogenesis: Overview

Atherogenesis involves a cascade of events (mainly top to bottom of this list, but with some feedback in reverse)

- High plasma apo B lipoproteins (Lp B = All non-HDL) **PLUS** focal endothelial trauma/dysfunction
- ↑ Infiltration of Lp B into the subendothelium (SE)
- ↑ Retention of Lp B in the SE
- ↑ Modification of Lp B in the SE
- ↑ Inflammation
- Plaque **rupture**
- **Thrombosis**
- ↓↓↓ **Blood flow**
- **Ischemic event**
Atherosclerosis Timeline

Progression in women lags by a decade

Endothelial dysfunction

In Utero through 1st decade
- Growth mainly by lipid accumulation

From third decade
- Smooth muscle and collagen

From fourth decade
- Thrombosis, hematoma

Adapted from Pepine CJ. Am J Cardiol. 1998; 82(suppl.10A):23S-27S.
Early Stages of Atherogenesis: Arterial Endothelium

**Healthy**

**Causes**
- Laminar flow
- *Lack* of Subendothelial Lp accumulation

**Effects**
- Anti-inflammatory
- Anti-oxidative
- Anti-thrombotic
- *(normal vasodilatation)*

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**Dysfunctional**

**Causes**
- *Turbulent* flow
- Subendothelial Lp *accumulation*

**Effects**
- Pro-inflammatory
- Pro-oxidative
- Pro-thrombotic
- *(abnormal vasodilatation)*

Early Stages of Atherogenesis: Apo B Lipos in Subendothelial Space

Contributions of Lp B (=LDL+ other Non-HDL Particles)

• **Lp B entry** into subendothelium ↔ **endothelial dysfunction**.

• **Lp B retention/binding** to subendothelial matrix – (proteoglycans, elastin, collagen)

• **Lp B Modification**
  – Lipolysis
  – Aggregation/fusion
  – Oxidation

• **Lp B uptake** by macrophages

Mechanism of Lipoprotein Retention: Role of Extracellular Matrix

- Lipoprotein retention is mediated by physical interaction between lipoproteins and matrix molecules\(^1,^2\)
  - Proteoglycans, collagen, elastin, fibronectin, vitronectin, etc
- Accessory molecules promote lipoprotein retention\(^1,^2\)
  - Lipoprotein lipase, secretory sphingomyelinase, secretory phospholipase A\(_2\)

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\(^1\) Adapted from Tabas I et al. *Circulation.* 2007;116(16):1832–1844.

Cardiovascular Risk Increases With Increased Plasma Apo B Lipoproteins

Rationale for therapeutic lowering of Lp B: to decrease the inflammatory response to retention

Atherosclerosis Timeline - Early Lesions

Not clear what determines progression vs. regression from fatty streak - Potentially reversible in utero

Adapted from Pepine CJ. Am J Cardiol. 1998; 82(suppl.10A):23S-27S.
**Middle Stages of Atherogenesis**

- Lipid-laden macrophages = foam cells
- Foam cells undergo apoptosis
- Foam cell apoptosis triggers:
  - ↑Macrophage recruitment
    - Monocyte adhesion and diapedesis thru endothelium
    - SMC chemotaxis and transformation
  - ↑Inflammation ↔ ↑Oxidation
  - ↑Lp B (=all Non-HDL) retention
  - ↑Lp B modification (various enzymes)
  - ↑Macrophage Lp B ingestion → foam cell
  - More foam cell apoptosis
Atherosclerosis: A Self-Feeding Inflammatory Cycle

Inflammatory Response to Atherogenic Lipoproteins

ICAM1 = intercellular adhesion molecule 1; oxLDL = oxidized low-density lipoprotein; VCAM1 = vascular cell adhesion molecule 1.

Middle-Late Atherosclerosis: Complex and Vulnerable Plaques

• Inflamed/apoptotic macrophages secrete matrix metalloproteases (MMP-9, etc)

• MMP effects:
  – Outward: remodeling of adventitia → vessel enlargement
  – Inward: erosion of collagen and elastin → thinning and weakening of the fibrous cap (plaque instability)
Atherosclerosis Timeline - *Middle Lesions*

Adapted from Pepine CJ. *Am J Cardiol.* 1998; 82(suppl.10A):23S-27S.
Arterial Remodeling

Late-Stage Atherosclerosis: Plaque Rupture and Acute Vascular Events

• Plaque rupture* due to
  – Matrix metalloproteases (MMP-9, etc)
  – Other inflammatory processes
  – Angiogenesis/neovascularization within the plaque
  – Mechanical effects

• Intra-arterial thrombosis:
  – Exposure of highly prothrombotic material (SE matrix, inflammation, etc.)
  – Pro-thrombotic state (plt. activation, increased soluble coag. factors)

• Acute ischemic event (MI, USA, CVA, sudden death, critical limb ischemia)

*Endothelial erosion may cause thrombosis w/o prior rupture, but these are mural thrombi, which are less likely to cause an acute CV event.
Unstable vs. Stable Plaque

**Unstable Plaque**
- 86% of Fatal MIs: < 70% prior stenosis
  - Large lipid core
  - Thin fibrous cap
  - ++macrophages
- 14% of Fatal MIs: > 70% prior stenosis
  - Small lipid core
  - Thick fibrous cap
  - ++SMCs

Clinical Manifestations of Different Types of Coronary Atherosclerosis

- Fixed stenosis → Stable angina
  *Gradual Progression—Less common*

- Plaque rupture → Unstable angina
  - Myocardial infarction
  - Sudden Death
  *Rapid Progression—More Common*
Up to 90% of AMI may be due to plaque rupture; AmHeartJ 1977;93:468.

Adapted from Pepine CJ. Am J Cardiol. 1998; 82(suppl.10A):23S-27S.
Regression of Atherosclerosis

• “Holy Grail” of atheroprevention (!?)
  – Plaque regression=“Nirvana”
  – Debates over “magic threshold” of LDL-C, non-HDL-C, HDL-C, CRP, etc.

• Not very useful if looking only at plaque thickness/size
  – Stability more important than size
  – Events can still occur with little or no stenosis
  – Events may be avoided just by stopping progression or ↓ growth

• Regression is a reasonable goal, but may be neither necessary nor sufficient to prevent CVD events
How Decreasing Plasma Lp B Levels Can Decrease Atherosclerosis and CV Risk

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Rationale for therapeutic lowering of Apo B lipoproteins: decrease the probability of inflammatory response to retention

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Rationale for therapeutic lowering of Apo B lipoproteins: decrease the probability of inflammatory response to retention

Atherogenesis: Prevention/Regression

- ↓ Plasma apo B lipoproteins (Lp B) PLUS ↓ focal endothelial trauma?
- ↓ Infiltration of Lp B into subendothelium (SE) PLUS increase LDL size
- ↓ Retention of Lp B in SE
- ↓ Modification of Lp B in SE
- ↓ Inflammation
- Prevention of plaque rupture
- Prevention of thrombosis
- No ↓↓ Blood flow
- No ischemic event
Summary:
Pathophysiology of Atherosclerosis

- Main elements are all interactive (multiple adverse feedback loops)
- Key areas of focus:
  - Apo B lipoproteins
  - Retention
  - Oxidation/modification
  - Inflammation
  - HDL to block/reverse above
- Stages:
  - Early—probably reversible
  - Middle—goal: regression vs. stabilization?
  - Late—main goal: stabilization of vulnerable plaques, prevention of new plaques
LIPID AND LIPOPROTEIN METABOLISM
Why Lipoproteins?

• Oil and water don’t mix
• *Lipids* (triglycerides, phospholipids, sterols) need vehicles (lipoproteins) to travel through *aqueous* media:
  – Lymph
  – Plasma
• Lipid transport (via lipoproteins) helps:
  – Absorb/distribute *dietary/intestinal* lipids
  – Re-distribute *endogenous* lipids
  – Energy use/storage—TG only
  – Cell structure—Chol, PL?
  – Cell function—Apo A-I, other?
Structure of a Typical Lipoprotein

- **Free cholesterol** *(surface and core)*
- **Phospholipid** *(amphipath at surface only)*
- **Triglyceride** *(core only)*
- **Apolipoprotein** *(amphipath at surface only)*
- **Cholesteryl ester** *(core only)*
Lipoprotein Classes: Physical Dimensions

CHYLCMICRON

KEY

* PHOSPHOLIPID
* FREE CHOLESTEROL
* TRIGLYCERIDE
* ESTERIFIED CHOLESTEROL

VLDL

"CORE" VOLUME = 524 x 10^6 Å^3
"SHELL" VOLUME = 68 x 10^6 Å^3

300 Å

> 1000 Å

20 Å Polar Shell

VLDL (range)

IDL

LDL (range)

HDL

"CORE" VOLUME = 41 x 10^6 Å^3
"SHELL" VOLUME = 13 x 10^6 Å^3

C.V. = 10.3 x 10^6 Å
S.V. = 5.6 x 10^6 Å

C.V. = 3.05 x 10^6 Å
S.V. = 2.67 x 10^6 Å

170 Å

100 Å
Lipoprotein Classes: Chemical Composition

CHYLOMICRON

IDL

LDL

HDL

VLDDL

KEY (%)

- PHOSPHOLIPID
- FREE CHOLESTEROL
- PROTEIN
- TRIGLYCERIDE
- CHOLESTEROL ESTER

- FREE CHOLESTEROL 2%
- PROTEIN 50%
- PHOSPHOLIPID 24%
- TRIGLYCERIDE 4%
- AND ESTERIFIED CHOLESTEROL 20%
# Lipids

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Lipophil.</th>
<th>Function</th>
<th>Location in Lipoprotein</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>+++</td>
<td>Energy</td>
<td>Core</td>
<td>Common</td>
</tr>
<tr>
<td>Free fatty acids</td>
<td>+++</td>
<td>Energy</td>
<td>Not in lipo; w/ albumin</td>
<td>Common</td>
</tr>
<tr>
<td>Chol-Ester</td>
<td>+++</td>
<td>Chol. storage</td>
<td>Core</td>
<td>Common</td>
</tr>
<tr>
<td>Free Chol</td>
<td>++</td>
<td>Membranes hormones</td>
<td>Inner shell + core</td>
<td>Common</td>
</tr>
<tr>
<td>Oxid Chol</td>
<td>+</td>
<td>Signaling?</td>
<td>Inner shell?</td>
<td>Rare</td>
</tr>
<tr>
<td>Plant Sterol</td>
<td>+</td>
<td>??</td>
<td>Inner shell?</td>
<td>Rare</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>+++/-- (amphip)</td>
<td>Structure</td>
<td>Shell</td>
<td>common</td>
</tr>
</tbody>
</table>
## Major Apolipoproteins

<table>
<thead>
<tr>
<th>Apo</th>
<th>Location</th>
<th>Function</th>
<th>Plasma Levels</th>
<th>Athero</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-I</td>
<td>HDL (Chyl)</td>
<td>Multi anti-athero</td>
<td>High</td>
<td>↓↓↓↓</td>
</tr>
<tr>
<td>A-II</td>
<td>HDL</td>
<td>??</td>
<td>Moderate</td>
<td>↓?</td>
</tr>
<tr>
<td>B-48</td>
<td>Chyl</td>
<td>Exog. TG &amp; Ch transp</td>
<td>Moderate (post-prandial only)</td>
<td>↑?</td>
</tr>
<tr>
<td>B-100</td>
<td>VLDL, LDL</td>
<td>Deliver endog. cholesterol</td>
<td>High</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>C-II</td>
<td>VLDL, HDL</td>
<td>↑LPL activity</td>
<td>Low</td>
<td>↓</td>
</tr>
<tr>
<td>C-III</td>
<td>VLDL, HDL</td>
<td>↓LPL, plq rupt?</td>
<td>Low</td>
<td>↑↑</td>
</tr>
<tr>
<td>E</td>
<td>VLDL, HDL</td>
<td>Remn Lp Catab, Chol Efflux?</td>
<td>Low</td>
<td>↑↑↑↑/↓?</td>
</tr>
<tr>
<td>(a)</td>
<td>Lp(a)</td>
<td>Ox FFA scaveng</td>
<td>Low</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

Apo B-100 and Apo A-I are most important clinically, but all are important.
### Lipoprotein Composition and Function

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Apolipoproteins</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons, Chylo-remnants</td>
<td>B-48 (A-I, C-II, C-III, and E)</td>
<td>Delivers TG &amp; Chol (intestinal or exog. path)</td>
</tr>
<tr>
<td>VLDL, IDL</td>
<td>B-100 (C-II, C-III, E)</td>
<td>Delivers TG &amp; Chol (endogenous path)</td>
</tr>
<tr>
<td>LDL</td>
<td>B-100</td>
<td>Delivers Chol (endogenous path)</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>B-100, apo (a)</td>
<td>Delivers Chol (endogenous path)</td>
</tr>
<tr>
<td>HDL</td>
<td>A-I, A-II (C-II, C-III, E)</td>
<td>Steroid horm. synth. Anti-infect, Anti-athero</td>
</tr>
</tbody>
</table>

*It is important to know all of these major lipoprotein fractions.*
# Fredrickson Hyperlipidemia Classification

## Plus 2

<table>
<thead>
<tr>
<th>Type</th>
<th>Lipoprotein in excess</th>
<th>Frequency</th>
<th>Athero</th>
<th>T Chol (mg/dL)</th>
<th>TG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>v. rare</td>
<td>sl ↑?</td>
<td>~1/6 TG</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>common</td>
<td>↑ to ↑↑↑</td>
<td>&gt;200</td>
<td>&lt;150</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL, VLDL</td>
<td>common</td>
<td>↑ to ↑↑↑</td>
<td>&gt;200</td>
<td>200-500</td>
</tr>
<tr>
<td>III</td>
<td>βVLDL, IDL</td>
<td>rare</td>
<td>↑↑↑</td>
<td>200-500</td>
<td>200-500</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>common</td>
<td>↑ to ↑↑</td>
<td>&lt;200</td>
<td>200-500</td>
</tr>
<tr>
<td>V</td>
<td>VLDL, Chylo</td>
<td>uncommon</td>
<td>↑ to ↑↑</td>
<td>~1/4 of TG</td>
<td>&gt;500</td>
</tr>
<tr>
<td>---</td>
<td>Lp(a)</td>
<td>uncommon</td>
<td>↑ to ↑↑↑</td>
<td>nl</td>
<td>nl</td>
</tr>
<tr>
<td>---</td>
<td>Low HDL</td>
<td>common</td>
<td>↑ to ↑↑↑</td>
<td>↓ to ↑</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

*All are worth remembering, but focus most on the common ones.*
Dyslipidemia and Disease

A. Pancreatitis—(↑↑↑TG + non-lipid causes only)
   1. ↑↑↑plasma TG + sl. leak of pancreatic lipase →
   2. Lipolysis →
   3. ↑↑↑FFA →
   4. Damage to pancreatic exocrine cells →
   5. Further leak of pancreatic lipase →
   6. Further lipolysis = vicious cycle

B. Atherosclerosis (#1 cause of death and disability)—most dyslipidemias are causal (adverse)
# Major Lipid/Lipoprotein Modifying Factors

<table>
<thead>
<tr>
<th>Name</th>
<th>Class</th>
<th>Function</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>CETP</td>
<td>Shuttle</td>
<td>CE for TG</td>
<td>Plasma</td>
</tr>
<tr>
<td>PLTP</td>
<td>Shuttle</td>
<td>PL transfer (HDL recombin.)</td>
<td>Plasma</td>
</tr>
<tr>
<td><strong>LPL</strong></td>
<td>Lipase</td>
<td>TG lipol. (Chyl, VLDL, IDL)</td>
<td>Vascular endothelium</td>
</tr>
<tr>
<td><strong>HL</strong></td>
<td>Lipase</td>
<td>TG&amp;PL hydrol (LDL, HDL)</td>
<td>Hepatic endothelium</td>
</tr>
<tr>
<td>EL</td>
<td>Lipase</td>
<td>Like HL?</td>
<td>Vascular endothelium</td>
</tr>
<tr>
<td>LpPLA2</td>
<td>Lipase</td>
<td>Cleaves Ox PL</td>
<td>LDL, HDL</td>
</tr>
<tr>
<td><strong>LCAT</strong></td>
<td>Esterifier</td>
<td>Chol ester.</td>
<td>HDL</td>
</tr>
</tbody>
</table>

*Focus on CETP, LPL, HL and LCAT only. Others are FYI.*
<table>
<thead>
<tr>
<th>Name</th>
<th>Class</th>
<th>Function</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPC1L1</td>
<td>Sterol transporter</td>
<td>Sterols into Enterocyte</td>
<td>Enterocyte</td>
</tr>
<tr>
<td>ABCG5/8</td>
<td>Sterol transporter</td>
<td>Plant Sterol out of enterocyte</td>
<td>Enterocyte</td>
</tr>
<tr>
<td>ACAT</td>
<td>Esterifier</td>
<td>FC to CE (C storage)</td>
<td>Intracellular</td>
</tr>
<tr>
<td>CEH</td>
<td>CE Hydrolase</td>
<td>CE to FC (C release)</td>
<td>Intracellular</td>
</tr>
<tr>
<td>ABCA1</td>
<td>Chol. Efflux</td>
<td>Chol to lipid poor Apo A-I particle</td>
<td>Cell surface</td>
</tr>
<tr>
<td>ABCG1</td>
<td>Chol. Efflux</td>
<td>Chol efflux to spherical HDL, etc.</td>
<td>Cell surface</td>
</tr>
<tr>
<td>SR-B1</td>
<td>Chol. Influx</td>
<td>Accepts chol from HDL (also donor?)</td>
<td>Cell surface</td>
</tr>
<tr>
<td>HSL</td>
<td>Lipase</td>
<td>Hydrolyze TG (rel. from adipocytes)</td>
<td>Intracellular (adipocytes)</td>
</tr>
<tr>
<td>PCSK9</td>
<td>LDL-R Chaperone protein</td>
<td>Targets LDL receptor for lysosomal degradation</td>
<td>Intra and extra-cellular</td>
</tr>
</tbody>
</table>

All are given FYI only: you do not need to memorize these!
*Enterohpetic* Cholesterol Transport (intestine to liver)

Liver

Dietary chol

**Intestine**

Intralumen Chol

Fecal neutral sterols

Biliary chol

Acetyl CoA

Chol

Remnant receptor

Chylomicron remnants

Chylomicrons

NPC1L1

Extrahepatic tissues

VLDL-C

IDL-C

LDL-C

LDL-R

LDL-R

LDL-R
Enterocyte Transport of Luminal Cholesterol (diet + bile)

Plant sterol has same paths as cholesterol (C) but much less net absorption
Plasma Metabolism of Intestinally-Derived Cholesterol

Lymph

Chylomicron

Chylomicron

Chylomicron remnant

TG

LPL

FA

Sk Muscle/Heart/Adipose tissue

Liver

Remnant receptor

Blood

Atherogenesis

Apo B-48
Apo E
Apo C-II
Lipoprotein lipase (LPL)
Remnant receptor
Endogenous Cholesterol Transport (liver to periphery to liver)

Liver

Dietary chol

Biliary chol

Intra-lumen Chol

Fecal neutral sterols

Intestine

Acetyl CoA

Chol

VLDL-C

IDL-C

LDL-C

Remnant receptor

Chylomicron remnants

Chylomicrons

NPC1L1

Extrahepatic tissues

Acetyl CoA

Chol

LDL-R

LDL-R

LDL-R

www.lipid.org
The Role of PCSK-9 in the Regulation of LDL Receptor Expression

LDL=low-density lipoprotein; LDL-R=LDL receptor; PCSK9=proprotein convertase subtilisin/kinexin type 9; SREBP-2=sterol regulatory element-binding protein-2.
Lipid and Lipoprotein Metabolism in the Normal Person

Glycerol
 DGAT2
 Fatty acids

Cholesteryl ester
 Triglyceride

VLDL
 (Very–low-density lipoprotein)
 TG:Cholesterol=5:1 ratio

Apo B

Liver
Lipid and Lipoprotein Metabolism in the Normal Person

Muscle and adipose tissue

Fatty acids

Lipoprotein lipase

Lipoprotein Lipase

Apo C-II enhances and apo C-III inhibits LPL activity

Apo B and apo E are ligands for LDL receptor

LDL (apo B,E) receptor clears VLDL, IDL & LDL

Bloodstream

IDL

LDL

VLDL

Liver

Hepatocyte

www.lipid.org
Metabolism and Atherogenicity of Apo B–Containing Lipoproteins\textsuperscript{1-4}

Liver

Dietary chol → Biliary chol

Intra-lumen Chol

Chylomicrons

NPC1L1

VLDL-C → IDL-C → LDL-C

Remnant receptor

Fecal neutral sterols

Chylomicron remnants

Acetyl CoA

Atherogenesis

Summary:
Lipid and Lipoprotein Metabolism

• Major Lipoproteins
  – Chylomicrons
  – VLDL → IDL → LDL
  – Lp(a) (origin/metabolic relationship to LDL unknown)
  – HDL

• Major Functions
  – TG transport (energy)—mainly Chylomicrons and VLDL
  – Cholesterol transport (cellular functions, hormone & bile synthesis) —mainly LDL and HDL
  – Anti-infective (anti-inflam, anti-athero)—mainly HDL
  – No known “primary” function for Lp(a)

• Disease Relationships
  – Pancreatitis
  – Atherosclerosis
  – Other?
Common Types of Atherogenic Dyslipidemia
Common Types of Atherogenic Dyslipidemia

• ↑TG + ↓HDL-C + small, dense LDL
  – 1\textsuperscript{o}: few \textit{monogenic}
  – 1\textsuperscript{o} + 2\textsuperscript{o}: many factors + polygenic
  – 2\textsuperscript{o}: many factors (↑Glucose, ↓thyroid, etc, etc.)

• ↑LDL-C
  – 1\textsuperscript{o}: FH and other \textit{monogenic}
  – 1\textsuperscript{o} + 2\textsuperscript{o}: Bad diet + polygenic
  – 2\textsuperscript{o}: few other factors

• Combination = mixed dyslipidemia
TG and HDL-C Both Contribute to CHD Risk

Adapted from Hopkins PN, et al. JACC 2005 Apr 5;45(7):1003-12.
Triglycerides Are Independently Associated With Premature Familial CHD*

*Triglyceride odds ratio adjusted for HDL-C; n=653 (Family History=early CHD), n=1029 (control). CHD=coronary heart disease; HDL-C=high-density lipoprotein cholesterol.

TG >150 mg/dL Increases CHD Risk Independent of LDL-C Level\textsuperscript{a}

PROVE IT-TIMI 22 Trial\textsuperscript{b}

- Achieving optimal TG (<150 mg/dL) may help reduce residual CVD risk in statin-treated post-ACS patients

\[\text{CHD Event Rate After 30 Days, %}\]

\[\begin{array}{c|c|c|c}
\hline
\text{LDL-C} & \text{TG <150} & \text{TG ≥150} \\
\hline
≥70 & 11.7\% & 15.0\% \text{ HR: 0.72 P=.017} \\
<70 & 16.5\% & 17.9\% \text{ HR: 0.84 P=.192} \\
\hline
\end{array}\]

\textsuperscript{a}Death, MI, and recurrent ACS

\textsuperscript{b}ACS patients on atorvastatin 80 mg or pravastatin 40 mg

Adjusted for age, gender, low HDL-C, smoking, HBP, obesity, diabetes, prior statin Rx, prior ACS.

Compared with LDL-C ≥70 mg/dL and TG ≥150 mg/dL, lower CHD risk was observed with low on-treatment TG (<150 mg/dL) and LDL-C (<70 mg/dL) (HR = 0.72; P = .017)

James Underberg, 4/15/2014
How Can Hypertriglyceridemia (HTG) Be Atherogenic?

- TGRL carry cholesterol and promote atherosclerosis (especially remnants)*
- VLDL is precursor to LDL (pro-atherogenic)
- HTG drives:
  - CE enrichment of VLDL (more atherogenic)*
  - ↓ LDL size (small, dense LDL are more atherogenic)*
  - ↓ LDL-C (small, dense LDL carry less cholesterol)*
  - ↓ HDL size (small, dense HDL are unstable and less anti-atherogenic)
- HTG is linked to other pro-atherogenic states*
  - Insulin resistance
  - Endothelial dysfunction
  - Pro-oxidative state
  - Pro-inflammatory state
  - Prothrombotic state

*Reasons why non-HDL-C is stronger than LDL-C as CVD factor.

CE=cholesteryl ester; TGRL=triglyceride-rich lipoproteins; VLDL=very low-density-lipoprotein.
Dyslipidemias Secondary to Hypertriglyceridemia

- Increased VLDL
- Hepatic lipase
- Increased triglycerides
- Rapid renal filtration of apo A-I
- Small, dense HDL
- Small, dense LDL
- Hepatic lipase

Bloodstream
Three Atherogenic Consequences of Hypertriglyceridemia

1. ↑TG/VLDL-C
2. SD LDL
3. ↓HDL-C

“Athero Dyslip”


CETP = cholesterol ester transfer protein
no arrow needed here. Small dense LDL formed but not necessarily more of them so would be hesitant to add the upward arrow.

James Underberg, 4/15/2014
Potential Impact of Small Dense LDL (pattern B)

And Associates with Metabolic Syndrome/DM: \( \downarrow \) HDL, \( \uparrow \) TG, \( \uparrow \) Inflam., \( \uparrow \) Thromb., \( \uparrow \) Oxid.

LDL-C Doubly Underestimates CVD Risk in Cases of Small, Dense LDL

Large LDL

Small, Dense LDL

Apo B

Cholesterol Ester

Fewer Particles & Less Risk/Particle

LDL-C 130 mg/dL

More Particles & More Risk/Particle

Lipid profile:

- TC: 198 mg/dL
- LDL-C: 130 mg/dL
- TG: 90 mg/dL
- HDL-C: 50 mg/dL
- Non–HDL-C: 148 mg/dL

Lipid profile:

- TC: 210 mg/dL
- LDL-C: 130 mg/dL
- TG: 250 mg/dL
- HDL-C: 30 mg/dL
- Non–HDL-C: 180 mg/dL

Adapted from Otvos JD, et al. Am J Cardiol. 2002;90:22i-29i.
High Triglycerides Are Strongest Predictor of Small, Dense LDL (Pattern B)

LDL=low-density lipoprotein; TG=triglyceride.

What Is Non–HDL-C?

non–HDL-C = Total cholesterol - HDL-C

Non–HDL-C Is Stronger than LDL-C in Predicting CHD Risk
The Framingham Study

(Average follow-up time was about 15 years)

• Within non–HDL-C levels, no association was found between LDL-C and the risk for CHD
• Strong, positive, graded association of non–HDL-C w/ CHD seen at every LDL-C level

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol.

Testing for Atherosclerosis/CVD Risk in HTG Patients

Required/Routine
- ↑TG level
- ↓HDL-C

Other Measures
- ↓LDL size (GGE, ultracentrifuge, NMR)
- ↑Non-HDL-C (=Total C – HDL-C)
- ↑Apo B-100
- ↑LDL-P (particle concentration, NMR only)
- ↑Remnant lipoproteins (RLP-C vs subfract)
- ↑VLDL-C & VLDL-C/TG (UC, “beta-quant”)
- ↑hsCRP (MetSynd surrogate)
LDL-C and Non-HDL-C

**LDL-C**
- Focus of most research
- Focus of current guidelines
- Always *reported* in lipid profile

**Non-HDL-C**
- Conceptually better (*all pro-athero lipos*)
- Stronger CVD factor
- Valid in HTG
- Valid non-fasting
- Always *measured* in lipid profile (“free”)

*Bottom line: Non-HDL-C is much better (no unique advantages of LDL-C) but we are stuck with LDL-C for now!*
Non-HDL-C and Apo B

Non-HDL-C

- **Cholesterol** content conceptually better (*causal* role)
- *Free* with lipid profile (*no* extra testing needed)
- Well standardized
- Already incorporated in guidelines

Apo B

- Apo B *may* play *causal* athero role
- Gives non-HDL particle count
- Good standardization
- Stronger CVD factor? (some dyslipidemias)
- Complementary to non-HDL-C?

**Bottom line:** Non-HDL-C cheaper/easier, best routine
Apo B likely gives ↑info but at ↑cost, ok as adjunct
Relations of LDL Particles and LDL Cholesterol to Levels of HDL Cholesterol and Triglycerides

*LDL-P Includes Remnants, Pools Lipid Risk in Metabolic Syndrome*

Framingham Offspring Study

Otvos JD. J Lab Medicine 2002;26(11/12):555-556.
LDL-P and Non-HDL-C

Non-HDL-C
- Includes all atherogenic particles
- *Free* with lipid profile
- Universally available
- Already incorporated into guidelines
- **Better** than LDL-P (w/ best apo B assay)

LDL-P
- *Well* studied
- Good CVD risk prediction (incl. some remnants)
- Well standardized
- *Beats* non-HDL-C (*some* studies)
- May suggest more aggressive Rx

*Bottom line: Non-HDL-C cheaper/easier, best routine
LDL-P gives ↑info but at ↑cost, ok as adjunct*
- **Lp(a) levels are genetically determined**
  - more kringle-repeats in gene →
  - longer apo(a) →
  - less apo(a) synthesis →
  - lower apo(a) levels

- Measurement important but difficult (protein vs chol?)

- **Pro-athero mechanisms of Lp(a):**
  - More oxidized (=more atherogenic) vs LDL
  - Scavenges and spreads oxidized FFAs
  - Pro-thrombotic? (plasmin competitor, ↑PAI-1 synth)
  - Slow LDL-R clearance (poor binding)

- ↑ in Acute Coronary Syndrome (why?)

HDL: Protective but Clinically Difficult
In HDL and all lipoproteins, unesterified cholesterol partitions between the core and inner aspect of the surface.
Pre-beta HDL is unique among lipoproteins in being non-spherical. Smaller, pre-beta-1 HDL is globular and has almost no lipid. Pictured here is pre-beta-2 HDL which is discoidal with apolipoproteins wrapped around a circular PL bilayer.

Low HDL-C associated with increased CHD Risk in observational data

*Data represent men age 50–70 yr from the Framingham Study.

Adapted from and reprinted with permission from Castelli WP. Can J Cardiol. 1988;4(suppl A):5A.
Low HDL-C & CVD events in TNT
In patients with LDL-C lowered to <70 mg/dL

Post-hoc, TNT Subjects w/ LDL-C ≤70 mg/dL on Statin\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>HDL-C Quintiles\textsuperscript{a}</th>
<th>Q1 (&lt;37)</th>
<th>Q2 (37 \text{ to } &lt;42)</th>
<th>Q3 (42 \text{ to } &lt;47)</th>
<th>Q4 (47 \text{ to } &lt;55)</th>
<th>Q5 (≥55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio Versus Q1\textsuperscript{*}</td>
<td>0.85</td>
<td>0.57</td>
<td>0.55</td>
<td>0.61</td>
<td></td>
</tr>
</tbody>
</table>

*On-treatment level (3 months statin therapy); n = 2661
\textsuperscript{b}Mean LDL-C, 58 mg/dL; mean TG, 126 mg/dL
\textsuperscript{*}P=.03 for differences among quintiles of HDL-C

Suggested Anti-atherogenic Mechanisms of HDL

- Promotes \textit{reverse cholesterol transport}
- Partner in TG metabolism
- \textbf{Antioxidant}
  - Oxidized \textit{in place of} apo B particles?
  - \textit{Reverses oxidation} of apo B particles?
- \textbf{Pro}-endothelial
  - \textit{↑} NO production
  - \textit{↑} Endothelial repair (\textit{↑}EC progenitors, other?)
- \textbf{Anti}-coagulant
  - Anti-thrombotic (\textit{↓}plt. membr cholesterol)
  - Pro-fibrinolytic
- \textit{↑} Prostacyclin production
- \textbf{Anti-inflammatory}
  - \textit{↓} Cell-adhesion molecules
  - Scavenges acute-phase reactants
  - \textit{↓} Neutrophil degranulation
  - Anti-complement?
  - Anti-T-cell effect?
- \textbf{Anti}-apoptotic (prevents death of MΦ, EC, SMC)
- Blocks other adverse effects of apo B particles?

The Role of HDL in Reverse Cholesterol Transport

ABCA1, ATP-binding cassette protein A1; CETP, cholesterol ester transfer protein; FC, free cholesterol; LCAT, lecithin:cholesterol acyltransferase; SR-A, scavenger receptor class A; SR-BI, scavenger receptor class B type I.

Antioxidant Effects Mediated by HDL

CE-OOX, oxidized cholesterol esters; GPX, glutathione peroxidase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; HODE, hydroxyoctadecadienoic acid; HPODE, hydroperoxyoctadecadienoic acid; LOOX, lipid hydroperoxides; PAF-AH, platelet-activating factor acetylhydrolase; PON, paraoxonase.

HDL–Mediated Inhibition of Adhesion Molecule Expression

MCP-1 = monocyte chemoattractant protein-1

Summary: HDL

Diagnosis
• HDL-C level likely best/sufficient
• Apo A-I, HDL-P, HDL\textsubscript{2}-C good, \textit{not} needed

Causes
• \textit{Common}: insulin resistance, HTG (mod-sev), \textit{poor} lifestyle (cigarettes, sedentary, central obesity), polygenic factors
• \textit{Rare}: monogenic, androgen abuse

Consequences
• HTG (mild-moderate)
• Athero/CVD (most \textit{common} dyslip. in CHD)

Treatment \textit{difficult} (by TLC or drug)
Key Take-Away Messages: Major Dyslipidemias

• Chylomicrons and chylomicron remnants (apo B-48, etc.)
  – Mainly for transport of dietary TG (energy)
  – Seen in fasting plasma only if TG > 1000 (T½=mins)
  – Increased risk of pancreatitis when TG > 1000
  – ~Always due to decreased clearance (↓LPL)
  – Minor role in atherogenesis (chylo remnants only)

• VLDL+IDL (apo B-100, apo Cs, apo E)
  – Common/moderate TG increase (TG 200-500)
  – Due to ↑production (fatty liver) + ↓clearance (↓LPL)
  – Moderate role in atherogenesis

• LDL (apo B-100)—also Lp(a) variant
  – Mainly for cholesterol transport
  – Major atherogenic factor
    • Oxidation/Inflammation
    • Endothelial dysfunction

• HDL (apo A-I, etc)
  – Major atheropreventive (blocks/reverses ~all adverse effects of VLDL, IDL, LDL)
Key Take-Away Messages: Major *Dyslipidemias* (cont.)

**Not associated** w/-Insulin-resistance

- $\uparrow$LDL alone (Type IIa)—common *and* high-risk

**Associated** w/ Insulin-resistance

- $\uparrow$VLDL (usually w/ $\downarrow$HDL; if w/o $\uparrow$LDL = type IV)—common *and* high-risk
- $\downarrow$HDL-C (usually w/ $\uparrow$VLDL)—common *and* high-risk
- Mixed dyslipidemia: $\uparrow$LDL + $\uparrow$VLDL + $\downarrow$HDL (IIb, IV or V)—common *and* high-risk