Cholesterol: Too Much and Too Little are Bad for Your Health

Robert D. Shamburek, MD

Senior Staff Clinician
Lipid Service, Cardiovascular and Pulmonary Branch
National Heart, Lung, and Blood Institute, NIH
Disclosures

Robert D. Shamburek, M.D

No Relevant Financial Relationships with Commercial Interests
Heart Attack

High Cholesterol
TC > 250 mg/dL

Pancreatitis

High Triglyceride
Trig > 1,500 mg/dL
The incidence of obesity in the U.S. population has increased greatly over the last decades resulting in development of multiple risk factors for CAD.

What has happened to David?
David

Sculpted by Michelangelo from 1501 to 1504
What has happened to David?

Quit exercising  (no more marathons)
Gave up Mediterranean diet  (Junk food)
High fat/carbohydrate diet
Drank excessive alcohol
Gained weight
David

Sculpted by Michelangelo from 1501 to 1504

Metabolic Syndrome

Articles.mercola.com/sites/articles/archive/2
Tabitha has picked up his bad habits
Diet and lifestyle play an important role in obesity and in atherosclerosis.
Development of Atherosclerotic Plaques

Normal

Fatty streak

Foam cells

Fibrous cap

Lipid core

Thrombus

Lipid-rich plaque
Atherosclerosis takes years or even decades to occur.

Development of Atherosclerosis

Secondary Prevention

Regression

Progression

Clinical Trial

Genetic Causes

High Cholesterol

Familial Hypercholesterolemia (FH)
TC = 1,000 mg/dL

Low Cholesterol

Abetalipoproteinemia
TC = 30 mg/dL
What is the role of lipoproteins (LDL, HDL) in lipid metabolism and atherosclerosis?

Atherosclerosis can occur with high LDL or with low HDL.
Oil in Water

Triglyceride in Plasma
Triglyceride = Energy

Cholesterol = Membrane stabilizer

Lipoprotein e.g. LDL, HDL

Triglyceride

Free Cholesterol (FC)

Cholesteryl ester (CE)

Lipoprotein e.g. LDL, HDL
LCAT (Lecithin Cholesterol Acyltransferase)

Phosphatidylcholine ("Lecithin") + Lysophosphatidylcholine

Lipoproteins → mature HDL

Cholesterol Ester (CE)
HDL Structure

Pre-beta Discoidal HDL

Alpha Spherical HDL

Delipidated apoAI ➔ Pre-beta Disc ➔ Alpha Spherical HDL

Free chol.

CE
Overview of Plasma Lipid Metabolism
Exogenous Pathway “food”

Endogenous Pathway “fasting”

Reverse Cholesterol Transport

Fasting Lipid Profile

Total cholesterol 270

**LDL** (direct or calculated*) “bad” 175

HDL “good” 31

Triglyceride 320

* Triglyceride <400 mg/dL

Friedewald equation

Total cholesterol = * LDL + HDL + VLDL (Trig/5)

* LDL = Total cholesterol – HDL – (Trig / 5)
Lipemic Plasma - Hypertriglyceridemia

Cream (chylomicron) intestine

Turbid (VLDL) liver
Present in Non fasting sample
**Lipoprotein Isolated by Electrophoresis (Charge) and Density**

**Figure 2. Schematic Representation of the Major Portions of the Lipoprotein Spectrum as Defined by Paper Electrophoresis, the Ultracentrifuge and by Immuno-electrophoresis Using Antisera Reacting with Both α and β Lipoproteins.**

The protein content is also depicted as in Figure 1.
Lipid Methyl Group Signal From Isolated Subclasses

Clin Lab Med 26:847-70, 2006

![Graph showing lipid methyl group signal from isolated subclasses. The graph compares the methyl chemical shift in ppm for VLDL, LDL, and HDL subclasses. The peaks are labeled with specific chemical shifts and wavelengths.](image-url)
LDL-C: 130 mg/dL
Risk

LDL-C: 130 mg/dL
Risk

LDL Cholesterol Balance
Lower risk

Large LDL (Pattern A)

LDL particle # 800

130 mg/dL

Higher risk

Small LDL (Pattern B)

LDL particle # 1,400

130 mg/dL

LDL particle # 1,000 normal

LDL Cholesterol Balance
Normal Ranges (10\textsuperscript{th}-90\textsuperscript{th} percentile) for NMR LipoProfile Parameters

<table>
<thead>
<tr>
<th>Lipoprotein parameter</th>
<th>Men (n = 4054)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>VLDL (nmol/L)</td>
<td></td>
</tr>
<tr>
<td>VLDL particles (total)</td>
<td>84.8 ± 67.0</td>
</tr>
<tr>
<td>Large VLDL/chylomicrons</td>
<td>3.4 ± 8.9</td>
</tr>
<tr>
<td>Medium VLDL</td>
<td>51.9 ± 55.2</td>
</tr>
<tr>
<td>Small VLDL</td>
<td>29.5 ± 26.3</td>
</tr>
<tr>
<td>LDL (nmol/L)</td>
<td></td>
</tr>
<tr>
<td>LDL particles (total)</td>
<td>1535 ± 490</td>
</tr>
<tr>
<td>IDL</td>
<td>28 ± 43</td>
</tr>
<tr>
<td>Large LDL</td>
<td>339 ± 241</td>
</tr>
<tr>
<td>Small LDL (total)</td>
<td>1169 ± 542</td>
</tr>
<tr>
<td>Medium small LDL</td>
<td>256 ± 116</td>
</tr>
<tr>
<td>Very small LDL</td>
<td>913 ± 433</td>
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<tr>
<td>HDL (μmol/L)</td>
<td></td>
</tr>
<tr>
<td>HDL particles (total)</td>
<td>28.1 ± 6.7</td>
</tr>
<tr>
<td>Large HDL</td>
<td>5.3 ± 3.5</td>
</tr>
<tr>
<td>Medium HDL</td>
<td>2.3 ± 3.4</td>
</tr>
<tr>
<td>Small HDL</td>
<td>20.5 ± 5.3</td>
</tr>
<tr>
<td>Mean particle sizes (nm)</td>
<td></td>
</tr>
<tr>
<td>VLDL size</td>
<td>52.3 ± 13.2</td>
</tr>
<tr>
<td>LDL size</td>
<td>20.4 ± 0.8</td>
</tr>
<tr>
<td>HDL size</td>
<td>8.7 ± 0.4</td>
</tr>
<tr>
<td>Calculated lipids (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Total triglycerides</td>
<td>157 ± 135</td>
</tr>
<tr>
<td>VLDL triglycerides</td>
<td>119 ± 134</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>121 ± 34</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>40 ± 14</td>
</tr>
</tbody>
</table>

Clin Lab Med 26:847-70, 2006
Increased VLDL

LIPOPROTEIN METABOLISM

Triglyceride 8000, **TC 400**

Triglyceride 400, **TC 400**

Triglyceride 100, **TC 400**
TRIGLYCERIDE METABOLISM IN FAMILIAL HYPERCHYLOMICRONEMIA

VLDL Triglyceride

Chylomicron Trig

Monoglycerides +
Diglycerides +
Free Fatty Acids

LPL
ApoC-II

Reactions marked with an X are inhibited in familial hyperchylomicronemia.
Unspun Lipemic Plasma

Normal plasma

Severe hypertriglyceridemia
## CHYLOMICRONEMIA SYNDROME  
(Feature 1 I Hyperlipoproteinemia)

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Lipemic plasma, lipemia retinalis eruptive xanthomas and recurrent pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein phenotype</td>
<td>Type I phenotype</td>
</tr>
<tr>
<td>Plasma lipids and lipoproteins</td>
<td>Elevated plasma triglycerides chylomicrons, and VLDL (5000 mg/dl)</td>
</tr>
<tr>
<td>Plasma apolipoproteins</td>
<td>Kindreds with LPL or apoC-II deficiency</td>
</tr>
<tr>
<td>Metabolic defect</td>
<td>Delayed clearance of triglyceride-rich lipoproteins</td>
</tr>
</tbody>
</table>
Pancreatitis in Children

High Triglyceride
Trig > 5,000 mg/dL
Lipemia retinalis
Does anyone here work with the apoE knockout mouse (apoE KO) as a model of atherosclerosis?
Increased IDL

LIPOPROTEIN METABOLISM

Liver

VLDL

LDL

Arterial Wall

Macrophage

Cholesterol Pool

ABCA1

CD36 SR-A

Oxidation

Increased IDL

Triglyceride 8000, TC 400

Triglyceride 400, TC 400

Triglyceride 100, TC 400
ApoE ISOFORMS

ApoE₃

ApoE₂

ApoE₄

NH₂ – Cys – Arg – COOH

NH₂ – Cys – Cys – COOH

NH₂ – Arg – Arg – COOH
Palmar Xanthoma

Tuberous Xanthoma
Heart Attack (30-40’s)

TC 400 mg/dL and Triglyceride 400 mg/dL
<table>
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<tr>
<th>Dysbetalipoproteinemia</th>
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<tbody>
<tr>
<td><strong>Clinical features</strong></td>
</tr>
<tr>
<td>Palmar and tuberous xanthomas, xanthelasma, and premature cardiovascular disease</td>
</tr>
<tr>
<td><strong>Lipoprotein phenotype</strong></td>
</tr>
<tr>
<td>Type III phenotype</td>
</tr>
<tr>
<td><strong>Plasma lipids and lipoproteins</strong></td>
</tr>
<tr>
<td>Elevated plasma cholesterol, triglycerides, VLDL, and IDL</td>
</tr>
<tr>
<td><strong>Plasma apolipoproteins</strong></td>
</tr>
<tr>
<td>Kindreds with apoE deficiency or apoE$_2$E$_2$</td>
</tr>
<tr>
<td><strong>Metabolic defect</strong></td>
</tr>
<tr>
<td>Delayed clearance of remnants of triglyceride rich lipoproteins</td>
</tr>
</tbody>
</table>
Increased LDL

LIPOPROTEIN METABOLISM

Liver

VLDL

IDL

LDL

Triglyceride 8000, TC 400

Triglyceride 400, TC 400

Triglyceride 100, TC 400

Arterial Wall Macrophage

CD36 SR-A

ABCA1

Cholesterol Pool
Arcus
Xanthelasma

http://www.cholesterolcholestrol.com/high-cholesterol-cholestrol-symptoms.html
Tuberous Xanthomas
Tendon Xanthoma

Achilles Tendon
Heart Attack (30-40’s)

High Cholesterol

TC 400 mg/dL and Triglyceride 100 mg/dL (LDL 350 mg/dL)
We have reviewed the disorders that increase the deposition of cholesterol on the arteries.

What removes the cholesterol from arteries?

- **LDL**
- **IDL**
- Triglyceride remnants
- **HDL**
SCHEMATIC OVERVIEW OF LIPOPROTEIN METABOLISM

Triglyceride → Muscle, adipose

Liver → Cholesterol

Cholesterol → Macrophage

ApoB → Triglyceride

ApoAl → Reverse Cholesterol Transport
LCAT (Lecithin Cholesterol Acyltransferase)

Phosphatidylcholine ("Lecithin")

Lysophosphatidylcholine

Cholesterol

Cholesterol Ester

FC

nascent HDL

mature HDL

"Acyl"
LIPOPROTEIN METABOLISM

Liver
LRP
LDLr
SR-BI

Liver

VLDL
LPL
E
CETP

IDL
HL
LPL

LDL
CD36
SR-A
Arterial Wall
Macrophage
ABCA1
Cholesterol Pool

Step 2
Step 1

25%
75%
The defect in the first step of Reverse Cholesterol Transport (RCT) is **ABCA1** (Tangier Disease)
LIPOPROTEIN METABOLISM

Liver

LRP

LDLR

SR-BI

VLDL

B

C-II

LPL

CE

IDL

E

LDL

B

Oxidation

CD36 SR-A

Cholesterol Pool

ABCA1

Arterial Wall Macrophage

FC

A-I

Nascent HDL

HDL

A-I

LCAT

HL

Nascent HDL

HDL

FC

HL

HDL <1
Histologic Findings in Tangier Disease

A. Tonsil
B. Bone marrow
C. Nerve
D. Smooth muscle cell

x 6,000  x 11,500  x 5,000  x 13,500
# TANGIER DISEASE

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Orange tonsils, cloudy cornea splenomegaly, intermittent neuropathy, and premature CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Lipids and Lipoproteins</td>
<td>HDL &lt; 5 mg/dL, LDL low and hypertriglyceridemia</td>
</tr>
<tr>
<td>Plasma Apolipoproteins</td>
<td>Decreased apoAI</td>
</tr>
<tr>
<td>Metabolic Defect</td>
<td>Rapid clearance of plasma HDL and apoAI</td>
</tr>
<tr>
<td>Genetic Defect</td>
<td>Defect in ABCA1 transporter</td>
</tr>
</tbody>
</table>
ABCA1 TRANSPORTER

Tangier Disease
SCHEMATIC MODEL OF CHOLESTEROL AND PHOSPHOLIPID EFFLUX FROM CONTROL AND TANGIER CELLS

CONTROL

TANGIER DISEASE

ABCA1
The defect in the second step of Reverse Cholesterol Transport (RCT) Is **LCAT deficiency**
LIPOPROTEIN METABOLISM

Liver

VLDL

IDL

LDL

Lp X particle

HDL <1

Kidney damage
| Clinical Features         | Cloudy cornea *(fisheye)*  
|                         | Renal disease              
|                         | No premature CAD           |
| Plasma Lipids and Lipoproteins | HDL < 5 mg/dL, LDL low  
|                            | hypertriglyceridemia, and  
|                            | Lp X particle              |
| Plasma Apolipoproteins   | Decreased apoAI            |
| Metabolic Defect         | Rapid clearance of plasma HDL  
|                          | and apoAI                  |
| Genetic Defect           | Defect in **LCAT** enzyme  
|                          | *(Lecithin:cholesterol acyltransferase)* |
“Fish eye”
Anemia
Target cells

Proteinuria
Renal failure (BUN, Creatinine)
Dialysis
Kidney transplant
Familial Lecithin:Cholesterol Acyltransferase Deficiency: First-in-Human Treatment with Enzyme Replacement

Decision tree for dose optimization

- Dose 1: 0.9 mg/kg
  - HDL-C > 40 mg/dL
    - Increase in HDL-C > 15 < 40 mg/dL
      - Dose 2: 0.9 mg/kg
        - Increase in HDL-C > 25 mg/dL
          - Dose 3: 0.3 mg/kg
            - Increase in HDL-C < 25 mg/dL
              - Dose 3: 0.9 mg/kg
                - Maintenance phase 9.0 mg/kg
                  10 doses weekly or biweekly
                  - Maintenance phase 3.0 mg/kg
                    10 doses weekly or biweekly

- Dose 2: 0.9 mg/kg
  - Increase in HDL-C > 25 mg/dL
    - Dose 2: 3.0 mg/kg
      - Increase in HDL-C < 25 mg/dL
        - Dose 3: 3.0 mg/kg
          - Dose 3: 9.0 mg/kg
Lipoproteins and Lipids During Dose Optimization Phase

Baseline 18%

A. HDL-C

B. LDL-C

D. Percent Cholesteryl Ester

H. Plasma Phospholipid

FPLC Analysis of Plasma Lipids Before and 24 Hours After rhLCAT Infusion

LCAT Deficiency

No HDL

LpX

Normal

HDL

No LpX

Lipoproteins and Lipids during Optimization (OPT) and Maintenance Phases

Baseline 18%

Maintained Increased Cholesterol Esters

Effect Cr, Cystatin C and BUN

Stabilized or improved renal function.

Effect of rhLCAT on HCT and Hemoglobin

Hemoglobin (nl > 13.7)

Hemoglobin (nl > 13.7) increased by 25%.

Hematocrit (nl > 40%)

Hematocrit (nl > 40%) increased by 25%.

Percent Change From Study Start

ICU

Percent change from study start showing an increase of 25%.

Day on Study

Conclusions

ACP-501 was well-tolerated with lipid changes that are consistent with increased HDL maturation.

Improvements in renal and hematological biomarkers in this patient support continued development of ACP-501 as enzyme replacement therapy for FLD.
Two Classical Intestinal and Liver Disorders Leading to Lipids Disorders
Abetalipoproteinemia – MTTP gene

Lipoprotein Metabolism – ApoB Lipoproteins

TC 40, HDL 35, LDL 0, Triglyceride 0
**Clinical features**
- Fat malabsorption, spinocerebellar ataxia, acanthocytosis and atypical retinitis pigmentosa.

**Plasma lipids and lipoproteins**
- Hypcholesterolemia, absence of chylomicrons, VLDL, and LDL.
- HDL only plasma lipoprotein, LDL 0, Triglyceride 0 (heterozygotes have normal plasma lipoproteins).

**Plasma apolipoproteins**
- Deficiency of plasma apoB-48 and apoB-100.

**Metabolic defect**
- Marked reduction in secretion of intestinal chylomicrons and liver VLDL. Fat soluble vitamin deficiency – vitamin E & A

**Genetic Defect**
- Defect in MTTP – microsomal triglyceride transfer protein
Liver - VLDL Secretion

ApoB

MTP

Vitamin E & A

Mature VLDL
Intestinal Cell

Vitamin E & A
Acanthocyte
Normal Intestinal cell

Fat in Intestinal cell
Neurological Deterioration

Abetalipoproteinemia

TC = 30 mg/dL and Triglyceride 0 mg/dL

Spinocerebellar ataxia

“Vitamin E deficiency”

Abetalipoproteinemia

TC = 30 mg/dL and Triglyceride 0 mg/dL
Peripheral bony spicules
Attenuated vessels
Macular scarring / atrophy
Optic nerve head pallor
Peripheral bony spicules
Atypical Retinitis Pigmentosa
“Vitamin A deficiency”
Sitosterolemia – ABCG5 / ABCG8 gene

Lipoprotein Metabolism – ApoB Lipoproteins

TC 450, HDL 35, LDL 400
Sterols

Cholesterol (animal)  Sitosterol (plant)

Egg  Seed
# SITOSTEROLEMIA

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Arcus, tendon xanthomas, and premature cardiovascular disease and arthritis</th>
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</thead>
<tbody>
<tr>
<td>Lipoprotein Phenotype</td>
<td>“Pseudo FH”</td>
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<tr>
<td>Plasma Lipids and Lipoproteins</td>
<td>Elevated plasma cholesterol and LDL</td>
</tr>
<tr>
<td></td>
<td>Elevated plant sterols (sitosterol)</td>
</tr>
<tr>
<td>Plasma Apolipoproteins</td>
<td>Increased plasma apoB</td>
</tr>
<tr>
<td>Metabolic Defect</td>
<td>Hyperabsorption of intestinal sitosterol and delayed biliary excretion</td>
</tr>
<tr>
<td>Genetic Defect</td>
<td>Defect on ABCG5 and ABCG8</td>
</tr>
</tbody>
</table>
ABC TRANSPORTERS

ABCG8 TRANSPORTER

ABCG5 TRANSPORTER

Sitosterolemia
CHOLESTEROL ABSORPTION AND ATHEROSCLEROSIS

Intestine

Enterocyte

Blood Vessel

Bile Acids

Bile Acid Transporter

Bile Acids

Bile Acid Transfer Protein

Cholesterol + β-sitosterol

NPC1L1

Sitosterol

ABCG5

ABCG8

Cholesterol + β-sitosterol

Cholesterol
LIPID METABOLISM AND ATHEROSCLEROSIS

GENETIC DEFECT IN β-SITOSTEROLEMA

Intestine

Enterocyte

Blood Vessel

Bile Acid Transporter

Bile Acids

Cholesterol + β-sitosterol

NPC1L1

Bile Acids

Bile Acid Transport Protein

Bile Acids

Bile Acid

Cholesterol + β-sitosterol

ABCG5

ABCG8
CHOLESTEROL ABSORPTION AND ATHEROSCLEROSIS

Intestine

Bile Acids

Cholesterol + β-sitosterol

Enterocyte

Bile Acid Transporter

Bile Acids

Bile Acid Transfer Protein

EZETIMIBE

NPC1L1

ABCG5

ABCG8

Cholesterol + β-sitosterol

Blood Vessel

Bile Acid

Cholesterol
CHOLESTEROL ABSORPTION AND ATHEROSCLEROSIS

Intestine

Enterocyte

Blood Vessel

Bile Acids

Bile Acid Transporter

Bile Acids

Bile Acid Transfer Protein

Cholesterol + β-sitosterol

EZE TIMIBE

NPC1L1

Cholesterol
How does dietary sitostanol work to lower cholesterol?
Intestinal Absorption of Sterols

- Micelles
- Diffusion barrier
- NPC1L1
- Ezetimibe
- ACAT2
- MMTP
- APO-B48
- ABCG5/G8
- LXRα
- Brush border membrane
- Basolateral membrane
- Chylomicrons
- Lumen
- Enterocyte
- Lymph
Intestinal Absorption of Sterols

Lumen | Enterocyte | Lymph

- **NPC1L1**
  - Chol
  - Sito

- **Ezetimibe**
  - Chol
  - Sito

- **ACAT2**
  - Chol

- **MMTP**
  - Chol

- **ABCG5/G8**
  - Sito

- **LXRα**

- **Chylomicrons**
  - Chol

- **Basolateral membrane**

**Brush border membrane**

**Diffusion barrier**
Sitostanol at the Grocery Store

**Benecol spread margarine**

- 0.85 grams of plant stanol esters per serving (1 tablespoon)

**Minute Maid Heart Wise**

- 0.4 grams of plant sterols per serving (8 fluid ounce)

**Promise activ Supershots**

- 2 grams of plant sterols per serving (100 ml)

**Low-fat extra-sharp Cheddar, Monterey jack and mozzarella**

- 0.65 grams of "phytosterol esters" per serving (1 ounce)
Whole grain and oat with CoraWise

0.8 grams of plant sterols in three slices

Dark- and milk-chocolate-covered almonds and raisins, and bars

1.1 to 1.5 grams of sterols per serving (1-ounce package)

Nature Valley Healthy Heart granola bars

0.4 grams of plant sterols per bar

Dark chocolate with pomegranate muffins

0.4 grams of plant sterols per serving (one 2-oz muffin)
Sitostanol at the Pharmacy

1.8 grams of plant sterols per tablet

2.1 grams of plant sterols per tablet
The $15,000 question?

PCSK9 inhibitor

Proprotein convertase subtilisin/kexin type 9
LDL 30, 90 or 200 mg/dL
PCSK9 With the Location of Naturally Occurring Mutations Associated with Elevated (top) or Reduced (bottom) Plasma Levels of LDL-C

A. Gain of function mutations

B. Loss of function mutations

*Phenotype depends on the population studied
Impact of an PCSK9 mAb on LDL Receptor Expression
PCSK9 Inhibitors

Praluent (alirocumab)  Sanofi/Regeneron
75 - 150 mg administered SQ once every 2 weeks

Repatha (evolocumab)  Amgen
150 mg administered SQ once every 2 weeks

$14,000 - 15,000 / year
Mechanisms of LDL-Lowering Therapies

- apoB
- TG
- MTP
- Chol
- LDLR
- PCSK9
- PCSK9 inhibitors
- Statins
- CAI
- BAS
- CE
- LDL
- B
- TG
- VLDL
- ASO
- MTP inhibitor

Cell Met 23:405-412, 2016
Proteins Regulating Lipoprotein Lipase Activity Are Therapeutic Targets

ApoC-III, ANGPTL3, and ANGPTL4 are all inhibitors of LPL activity and thus candidates for therapeutic inhibition. ApoA-V is a stimulator of LPL activity and thus a candidate for upregulation or augmenting its activity.
Novel Therapies for Severe Dyslipidemia Originating from Human Genetics

**Targets**
- DNA
- Transcription
  - Primary transcript
- Post-transcriptional processing
  - Mature mRNA
- Translation
  - Protein (inactive)
- Post-translational processing
  - Modified protein (active)
- Protein targeting and transport
- Metabolic pathways

**Approaches**
- AAV-based gene therapy
- CRISPR/Cas9
- PCSK9 CRISPR-Cas9
- Mipomersen* (apoB), Volanesorsen (apoCIII), IONIS-APO(a)^{-}LTAG, IONIS-ANGPTL3-LTAG, DGAT2-ASO
- ASO (single-stranded DNA)
- siRNA
- Enzyme replacement
- Recombinant protein
- Peptide mimetics
- Cell-penetrating peptides and cargo molecules
- Novel therapies
- ApoE, ApoCII, CER-001 (HDL)
- ACP-501 (LCAT)
- CAT-2000 series (SREBP)
- Evanocumab (ANGPTL3)
- Evolocumab* (PCSK9)
- Alirocumab* (PCSK9)
- Bococizumab (PCSK9)
- Lomitapide* (MTP inhibitor), New omega-3
- Monoclonal antibodies
- PPAR delta agonists
- Metabolic modifiers (different mechanisms)

**Novel therapies**
- Alipogene tiparovec (LPL), AAV8-LDLR
- PCSK9 (ALN-PCSSC)
- Sebelipase alfa (LAL)
- ApoE, ApoCII, CER-001 (HDL)
- CAT-2000 series (SREBP)
- Evanocumab (ANGPTL3)
- Evolocumab* (PCSK9)
- Alirocumab* (PCSK9)
- Bococizumab (PCSK9)
- Lomitapide* (MTP inhibitor), New omega-3
- Monoclonal antibodies
- PPAR delta agonists
- Metabolic modifiers (different mechanisms)
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The Patients

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5NW Metabolic Ward
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- Nora Quade
- Raven McGlotten
- Pamela Orzechowski

Pacific Biomarkers