**Beyond the Numbers**

Lipid Control Webinar Series

**Mended Hearts**’ mission is “to inspire hope and improve the quality of life of heart patients and their families through ongoing peer-to-peer support, education and advocacy.”

**The National Lipid Association’s (NLA)** mission is “to enhance the practice of lipid management in clinical medicine.”

**The Foundation of the NLA’s** mission is “to improve the welfare of patients and families affected by cholesterol and triglyceride problems.”
Before we begin

- All attendees are in listen-only mode
- If you cannot hear, check the audio button on your personal computer to assure the sound is on.
- Please type your questions into the Q&A box at any time during the presentation. Questions will be read and answered after the presentation.
  - Note: The presenter will not be able to answer questions about you, specifically, or about your child, as he/she is not the treating physician.
- The PDF version of the slides, as well as the recording of this presentation, will be available on the Mended Hearts website following the event.
Beyond the Numbers
Lipid Control Webinar Series 2021

Catherine J. McNeal, MD, PhD
Assoc. Prof of Internal Medicine & Assoc. Prof of Pediatrics
Texas A&M University System Health Science Center-College of Medicine
Division of Cardiology, Baylor Scott & White Health
Temple, TX

Mandy Sandkuhler
Patient Representative

Andrea Baer, MS, BCPA
Executive Director
Mended Hearts
Before we get started, please respond to our brief polling questions as they present on screen.
Poll #1

What is TRUE about lipoprotein(a)?

a. Like LDL-Cholesterol, it is greatly affected by your diet
b. It is primarily inherited from your parents
c. Like HDL-Cholesterol, it is a “good” lipid
d. Not sure - I do not know what lipoprotein(a) is
What would happen to all those Cardiologists if...
...If no one developed heart disease*??

*AKA

Atherosclerosis (AS),
Atherosclerotic cardiovascular disease (ASCVD)
Cardiovascular Disease (CVD)
Coronary Heart Disease (CHD)
“Hardening of the Arteries”
Coronary Heart Disease

Caused by the buildup of cholesterol (plaques) in the heart arteries (not veins) that nourish the heart muscle and slows down or prevents blood flow in these arteries.

Lack of blood flow causes decreased oxygen supply to the heart muscle (ischemia).

Ischemia causes pain (angina).

Prolonged ischemia causes heart muscle to die = heart attack (myocardial infarction).

ASCVD and CVD includes strokes and peripheral arterial disease.
What are “plaques” and how do they form?

Plaques refer to the deposits of cholesterol, cells and their debris in the artery walls.

Because of many factors, these deposits preferentially form in arteries not veins.

If there are plaques in the coronary (heart) arteries, there can be plaques in other arteries (those going to the brain, in the legs).

Plaques are essential precursors to a heart attack.
Atherosclerotic Plaque Development
Risk Factors for ASCVD

Risk Factors are not additive.

They multiply each other’s effects
Major Risk Factors For Atherosclerosis (CHD)

- High Cholesterol (LDL-c)
- Low Cholesterol (HDL-c)
- High blood pressure
- Diabetes (Type I or Type II)
- Tobacco use
- Male sex
- Age
Emerging Risk Factors

Lipoprotein(a)

Apolipoprotein B

Dozens of others (!)
“Cholesterol is good for you. It clogs your veins so you don’t bleed as much when you get a cut!”
What is cholesterol and why worry about it?

What is it?
• $C_{27}H_{45}OH$ (Yikes!!!)
• A type of fat in the blood. It is essential for good health especially forming the walls of cells in the body including nerve cells, sex hormones, and vitamins that are key to normal growth and development.
• About 30% of cholesterol comes from foods we eat (egg yolks, saturated and unsaturated fats). It is also made by your body.
• Carried in the blood by “lipoproteins”

“Lipids” (as in a lipid panel or lipid test) are fats in the blood and include cholesterol and triglycerides. These are two very different fats.
Cholesterol

Why worry about it?

• The excess LDL cholesterol and/or lipoprotein(a) cholesterol in the blood that is not being used by your body can infiltrate the artery walls and form deposits or ‘plaques.’
• Plaque build up can eventually lead to heart attacks, stroke and blockage of the leg arteries.
• HDL cholesterol functions like a vacuum cleaner to reduce the cholesterol deposits/plaques in the arteries.
"Anti-atherogenic"  
"Heavenly/Healthy"  
HDL-C  

ApoB Containing Lipoproteins  
"Lousy/Lethal LDL-C  

HDL  

LDL  

Remnants  

Lp(a)  

Stable plaques  

Thrombosis  

Inflamed unstable plaques
The Math
What is included in a lipid panel?

The Total Cholesterol (TC) includes:

1. **LDL-cholesterol** AKA as the “bad” cholesterol. An easier way to think of it is as the “Lousy” or “Lethal” cholesterol which should be Low. The Lower LDL-C is, the better it is for your heart (and brain).

2. **HDL-cholesterol** AKA the “good” cholesterol. An easier way to think of it is as the “Healthy” or “Heavenly” cholesterol which should be High. The higher the HDL-C is (usually) the better it is for your heart (and brain).

3. But why doesn’t the LDL-C and HDL-C ADD UP to the Total cholesterol?
The Math

\[ TC = HDL-C + LDL-C + VLDL-C + \text{lipoprotein}(a)-C + \text{Remnant cholesterol} \]

\[ \text{VLDL-C} \] is a little “lousy”. Some labs reports will include the calculated VLDL-C

\[ \text{Lp(a)-C} \] is “lousier” than the “lousy” cholesterol

Rearranging the above equation:

\[ TC - HDL-C = LDL-C + VLDL-C + \text{Lp(a)-C} + \text{Remnant Cholesterol} \]

Everything in red that is NOT HDL-C is called NON-HDL-C in a report and is atherogenic (promotes plaque buildup)
Triglycerides

This is a type of fat found in the blood that provides some of the fuel to help with daily activities (sugar (AKA glucose) is the other fuel).

Much of the triglycerides in our bloodstream comes from what we eat (sugars and starches), although the body also makes triglycerides. Triglycerides not immediately needed are stored in fat cells to be used later as fuel. While triglycerides are important for your body’s normal function, high levels of triglycerides can cause health problems and are commonly elevated in people with prediabetes or diabetes.
The Math
What is measured?

- In a lipid panel, the total cholesterol, HDL-cholesterol and triglyceride level is measured in the lab.

- The VLDL-cholesterol is estimated by:
  - Triglyceride level/5 OR
  - The Martin Hopkins equation

- In patients with an elevated Lp(a) protein level, the Lp(a)-cholesterol is included in the LDL-C.
Lipoproteins
“Fat-Carrying Proteins”

Lipoproteins also carry triglycerides. Some advanced lipoprotein tests also measure LDL-TG, VLDL-TG and HDL-TG.

Low Density Lipoprotein
LDL-C is the cholesterol carried by the LDL particle

High Density Lipoprotein
HDL-C is the cholesterol carried by the HDL particle

(Triglycerides are hidden)
What are optimal levels?

The Lousy (LDL) cholesterol should be Lower than 100 mg/dl (but lower levels may be desired for people with ASCVD)

The Heavenly cholesterol should be Higher than 50 mg/dL

The other lipid, the triglyceride level should be less than 150 mg/dl
When Should You Check Cholesterol?

**All adults** after the age of 20 years and every 5 years if normal, more frequently if elevated and/or if cholesterol-lowering medications are started

**Children** after the age of 2 years if:
- Parent with high cholesterol
- Parent or grandparent with early cardiovascular disease

**All children** starting at 9-11 years old
Why do I need to fast?

Triglycerides are increased when you are not fasting.

Because VLDL-C is often estimated by TG/5, if you are not fasting it will be higher and therefore the TC will be higher.
“Good news.
Your cholesterol has stayed the same, but the research findings have changed.”
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin

Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

Age 40-75 y and
LDL-C ≥270<190 mg/dL (≥7.8-<4.9 mmol/L)
without diabetes mellitus
10-year ASCVD risk percent begins risk discussion

LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)

Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)

Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)

Age >75 y
Clinical assessment, Risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, pericarditis, HIV)
- Ethnicity (e.g., South Asian ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides ≥175 mg/dL, ≥2.0 mmol/L

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 mmol/L
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)

<5% “Low Risk”

5% - <7.5% “Borderline Risk”

≥7.5% - <20% “Intermediate Risk”

≥20% “High Risk”

Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)

Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)

Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy...
### Risk-Enhancing Factors for Clinician-Patient Risk Discussion

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history of premature ASCVD</strong> (males, age &lt;55 y; females, age &lt;65 y)</td>
</tr>
<tr>
<td><strong>Primary hypercholesterolemia</strong> (LDL-C 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*</td>
</tr>
<tr>
<td><strong>Metabolic syndrome</strong> (increased waist circumference [by ethnically appropriate cutpoints], elevated triglycerides [&gt;150 mg/dL, nonfasting], elevated blood pressure, elevated glucose, and low HDL-C [&lt;40 mg/dL in men; &lt;50 mg/dL in women] are factors; a tally of 3 makes the diagnosis)</td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong> (eGFR 15–59 mL/min/1.73 m² with or without albuminuria; not treated with dialysis or kidney transplantation)</td>
</tr>
<tr>
<td><strong>Chronic inflammatory conditions</strong>, such as psoriasis, RA, lupus, or HIV/AIDS</td>
</tr>
</tbody>
</table>
## Risk-Enhancing Factors for Clinician-Patient Risk Discussion (cont’d)

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia</td>
</tr>
<tr>
<td>- High-risk race/ethnicity (e.g., South Asian ancestry)</td>
</tr>
<tr>
<td>- <strong>Lipids/biomarkers</strong>: associated with increased ASCVD risk</td>
</tr>
<tr>
<td>- Persistently elevated (optimally 3 measurements) primary hypertriglyceridemia (≥175 mg/dL, nonfasting);</td>
</tr>
<tr>
<td>- If measured:</td>
</tr>
<tr>
<td>- Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)</td>
</tr>
<tr>
<td>- <strong>Elevated Lp(a)</strong>: A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).</td>
</tr>
<tr>
<td>- Elevated apoB (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C &gt;160 mg/dL and constitutes a risk-enhancing factor</td>
</tr>
<tr>
<td>- ABI (&lt;0.9) *</td>
</tr>
</tbody>
</table>
Lp(a): the Triple Threat
Lipoprotein(a)

Danish kringle

Kringle IV-2 copy number variant: 2 to >40 repeats

apolipoprotein(a)

Apolipoprotein B
One on each LDL particle

LDL-like particle
Pathophysiology: A Triple Risk Factor

1. Thrombosis

2. Atherosclerosis

3. Calcific aortic valve disease

Wound healing

Fibrinolysis inhibition

Foam cells, inflammation, oxidized phospholipids

Physiology

Nordestgaard 2018
Lipoprotein-a Genetics

- More than 90% of the Lp(a) concentration is explained by inheritance.
  - You can inherit one gene from each parent
- The gene is fully expressed by 1-2 years of age.
- Reaches adult levels by ~5 years of age.
- Levels are stable throughout the lifespan, independent of age, gender or lifestyle habits although after menopause levels may increase slightly.
Use of lipoprotein(a) in clinical practice: A biomarker whose time has come—A scientific statement from the National Lipid Association. Don P. Wilson, MD, on behalf of the Writing group

Don P. Wilson, MD*, Terry A. Jacobson, MD, Peter H. Jones, MD, Marlys L. Koschinsky, PhD, Catherine J. McNeal, MD, PhD, Børge G. Nordestgaard, MD, DMSc, Carl E. Orringer, MD
Due to the severe and lifelong exposure, those with abnormally high levels of lipoprotein (a) often develop “clogged arteries”.

This ultimately causes damage by reducing blood flow to organs, including the heart and brain. This damage can result in a heart attack or stroke at a very early age (for example 40-50 years of age or younger).

While symptoms of “clogged arteries” don't usually occur during childhood, the risk of experiencing health problems as children with high levels of lipoprotein (a) become adults is very high.
Clots can also occur in arteries with atherosclerosis. Abnormally high blood levels of lipoprotein (a) can interfere with the way the body “dissolves” these blood clots, potentially reducing blood flow to the heart and brain. When a clot forms in a clogged artery and is not dissolved properly, the decreased blood flow to the heart and brain may result in a heart attack or stroke.
Lipoprotein Buckets

Calculated LDL-CHOL
Non-HDL-CHOL
Example

LDL-C = 192 mg/dL:

Cholesterol in the buckets

Lp(a) = 124 mg/dL:

Number of buckets (like apoB)
“It’s easy to tell the difference between good cholesterol and bad cholesterol. Bad cholesterol has an evil laugh.”
Therapies for Lp(a)
# Lp(a) lowering therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Reduction in Lp(a)</th>
<th>Mechanism/problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>0 to ↑ 7%</td>
<td>No Effect on Lp(a) protein level/ Decreases ASCVD risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduces Lp(a) protein level</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓ 25%</td>
<td>No effect on ASCVD risk reduction so rarely used</td>
</tr>
<tr>
<td>PCSK9 inhibitor</td>
<td>↓ 25%</td>
<td>Decreased Lp(a) formation?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Increased catabolism?)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreases ASCVD risk</td>
</tr>
<tr>
<td>Apheresis</td>
<td>↓ 35%</td>
<td>Removal of apoB lipoproteins (For severe cases)</td>
</tr>
<tr>
<td>New: Apo(a) antisense</td>
<td>↓ 90%</td>
<td>Decreased hepatic apo(a) synthesis</td>
</tr>
</tbody>
</table>
Case Presentation

• 42-yr-old male law enforcement officer referred for evaluation of hyperlipidemia.
• Cardiac history: No angina symptoms, average exercise tolerance
• Recently diagnosed HTN, snuff use
• Family history: Mother with a stent at age 62 and doing well at age 69. He thinks she has a high cholesterol. Father (70) has T2DM, and sister (45) has no medical problems but did have gestational DM. He has 2 children age 18 and 16.
• Exam: BP 144/88, BMI 32 kg/m2, soft heart murmur.
• Baseline labs: TSH, renal, hepatic function are normal
Case Presentation Cont:

• A1C 6.4% (No Rx)
• Lipids:
  • Lp(a) 124 mg/dL
  • TC 261 mg/dL (No RX)
  • HDL-C 42 mg/dL,
  • TG 132 mg/dL,
  • LDL-C + Lp(a)-C 192 mg/dL
  • non-HDL-C  219 mg/dL
• Coronary Artery Calcium score 950, >90%tile for age and gender
• Echo: Aortic valve sclerosis with mild stenosis
• His mother, sister and two children were also found to have an elevated Lp(a) level
He was started on rosuvastatin and the "LDL-C" dropped to 126 mg/dL

Ezetimibe was added and the "LDL-C" dropped to 88 mg/dL

Aspirin was started

He was referred to a dietician

His children were referred to a pediatric lipid specialist
Lipoprotein(a): key points

• Lp(a) cholesterol is comeasured in LDL-C
• Screen to improve cardiovascular disease risk estimation in primary and secondary prevention patients and those with calcific aortic valve disease
• Screen family members
• Treat with statin therapy first, ezetimibe second, consider PCSK9i if very high risk
Advanced Lipoprotein Analyses

There are a number of different lipoprotein analyses other than a lipid panel but many professional societies argue that they may not provide information about the ASCVD risk assessment beyond the standard lipid panel. Not all insurance companies cover these analyses. Some of the more common tests include:

• **ApolipoproteinB** (apoB): ApoB is the protein found on the LDL particle. Since there is one ApoB in each LDL and Lp(a) particles, this is a measure of how many “atherogenic” particles there are. Measuring ApoB can be especially helpful if the triglycerides are elevated.

• **NMR lipoprotein testing**: This test can provide information about the number and size of each lipoprotein.

• **Lipoprotein Metabolism Profile**: This test is useful to aid in identifying the cause of a cholesterol or triglyceride elevation.
Poll #2

What is TRUE about lipoprotein(a)?

a. Like LDL-Cholesterol, it is greatly affected by your diet
b. It is primarily inherited from your parents
c. Like HDL-Cholesterol, it is a “good” lipid
d. Not sure - I do not know what lipoprotein(a) is
Poll #3

Based on my participation in this webinar, I:

a. Learned something new that has inspired me to make changes
b. Need more information before I will make any changes
c. My routine is already consistent with what is recommended
d. Will not make changes / Do not agree with recommendations
For additional questions, please email: Andrea.baer@mendedhearts.org

Join us for the next session of the series:
**Your Doctor Prescribed You What? A Review of Lipid-Altering Therapies**
April 13, 2021 at 3:00 PM ET

Presenter: Zareen Farukhi, MD, MPH
Patient: Robert Brai
Moderator: Andrea Baer, MS, BCPA

This webinar series is brought to you by Mended Hearts®, The National Lipid Association (NLA), and The Foundation of the NLA. This activity is supported by Amgen, Esperion and Novartis.