The Benefits of Early and Aggressive Lowering of LDL-Cholesterol

June 18, 2020 at 2:00 PM EST
Presenter: Nihar Desai, MD
Moderator: Andrea Baer, MS, BCPA
**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.”
Beyond the Numbers
Lipid Control Webinar Series

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Beyond the Numbers:
*The Benefits of Early and Aggressive Lowering of LDL Cholesterol*

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• Medical review committee for Anthem.
Roadmap

• Review the relationship between LDL-C, atherosclerotic cardiovascular disease and adverse events.

• Emphasize the importance of early management of hypercholesterolemia for preventing heart disease and aggressive LDL-C control for avoiding any further events.

• Discuss recent clinical trial results that have informed our understanding of benefits of lowering LDL-C with statin and non-statin therapies and how they have shaped practice guidelines.
The Central Role of Lipids in Atherosclerosis
The Central Role of Lipids in Atherosclerosis

Population Attributable Risk From Various Modifiable Risk Factors on Acute MI
(Overall Population)¹

**RISK FACTORS**

PAR=population attributable risk, which indicates the number or proportion of cases that would not occur in a population if the risk factor were eliminated.²

PARs from individual risk factors are reported. Note that the sum of individual PARs is greater than 100% because “cases” can simultaneously be attributed to more than one risk factor and be counted twice. PAR percentages reflected here do not indicate the amount of risk that would decrease by addressing the identified risk factors.¹

¹Irregular consumption of fruits and vegetables; ¹A model-dependent index combining positive exposure to depression, perceived stress at home or work (general stress), low locus of control, and major life events, all referenced against non-exposure for all 5 factors. ²ApoB/ApoA1 ratio; INTERHEART study; n=15,152 patients and 14,820 controls in 52 countries.¹

Apo=apolipoprotein; MI=myocardial infarction.

The Cumulative Effect of Hypercholesterolemia

Cumulative exposure (cholesterol yrs) by age:
FH vs. unaffected (healthy) individuals

HoFH  HeFH  Unaffected individuals

Threshold for CHD:
Reached by age 20 in for those with HoFH;
>60 in healthy individuals

## ASCVD Risk Estimator

### Lifetime ASCVD Risk: 39%  
Optimal ASCVD Risk: 2.5%

<table>
<thead>
<tr>
<th>Current Age</th>
<th>Sex</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td>Male</td>
<td>White</td>
</tr>
</tbody>
</table>

- **Systolic Blood Pressure (mm Hg):** 138
- **Diastolic Blood Pressure (mm Hg):** 86
- **Total Cholesterol (mg/dL):** 220
- **HDL Cholesterol (mg/dL):** 34
- **LDL Cholesterol (mg/dL):** 150

- **History of Diabetes:** Yes
- **Smoker:** Current
- **On Hypertension Treatment:** Yes
- **On a Statin:** Yes
- **On Aspirin Therapy:** Yes
2019 ACC/AHA Guideline on 1° Prevention of CV 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 ≥70-<190 mg/dL (≥2.1-<4.9 mmol/L)**
  - Without diabetes mellitus
  - 10-year ASCVD risk percent begins risk discussion

- **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, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

### Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/dL, ≥4.5 mmol/L)

### Risk Discussion:
- **<5% “Low Risk”**
  - Emphasize lifestyle to reduce risk factors (Class I)

- **5%-<7.5% “Borderline Risk”**
  - Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

- **≥7.5% -<20% “Intermediate Risk”**
  - Risk discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30%-49% (Class I)

- **≥20% “High Risk”**
  - 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
2019 ACC/AHA Guideline on 1° Prevention of CV 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

- **Age 40-75 y and LDL-C ≥160 mg/dL (≥4.1 mmol/L)**
  - Consider statin if family history of premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- **Age >75 y**
  - Clinical assessment, Risk discussion

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)

**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, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

**Lipid/biomarkers:**
- Persistently elevated triglycerides (≥175 mg/dL, ≥4.5 mmol/L)

In selected individuals if measured:
- hs-CRP ≥1.0 mg/L
- Lp(a) levels ≥50 mg/dL or ≥125 mmol/L
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

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**Risk discussion:**
- 5% – <7.5% “Borderline Risk”
- ≥7.5% – <20% “Intermediate Risk”
- ≥20% “High Risk”

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

**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
Reducing LDL-C Reduces CV Events

% Patients with CHD Event

LDL-C achieved mg/dL

Primary prevention trials
Secondary prevention trials
HPS

PL = placebo
Rx = active treatment

## Reducing LDL-C Reduces CV Events

### Statin v. Control

<table>
<thead>
<tr>
<th>Event</th>
<th>Statin</th>
<th>Control</th>
<th><strong>Relative risk (CI) per mmol/L LDL-C reduction</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>2310 (0.9%)</td>
<td>3213 (1.2%)</td>
<td>0.74 (0.69 - 0.78)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1242 (0.5%)</td>
<td>1587 (0.6%)</td>
<td>0.80 (0.73 - 0.86)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3380 (1.3%)</td>
<td>4539 (1.7%)</td>
<td>0.76 (0.73 - 0.79)</td>
</tr>
<tr>
<td>CABG</td>
<td>816 (0.3%)</td>
<td>1126 (0.4%)</td>
<td>0.76 (0.69 - 0.83)</td>
</tr>
<tr>
<td>PTCA</td>
<td>601 (0.2%)</td>
<td>775 (0.3%)</td>
<td>0.78 (0.69 - 0.89)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1686 (0.6%)</td>
<td>2165 (0.8%)</td>
<td>0.76 (0.70 - 0.83)</td>
</tr>
<tr>
<td>Any coronary revascularisation</td>
<td>3103 (1.2%)</td>
<td>4066 (1.6%)</td>
<td>0.76 (0.73 - 0.80)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>987 (0.4%)</td>
<td>1225 (0.5%)</td>
<td>0.80 (0.73 - 0.88)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>188 (0.1%)</td>
<td>163 (0.1%)</td>
<td>1.10 (0.86 - 1.42)</td>
</tr>
<tr>
<td>Unknown stroke</td>
<td>555 (0.2%)</td>
<td>629 (0.2%)</td>
<td>0.88 (0.76 - 1.02)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1730 (0.7%)</td>
<td>2017 (0.8%)</td>
<td>0.85 (0.80 - 0.90)</td>
</tr>
<tr>
<td><strong>Any major vascular event</strong></td>
<td><strong>7136 (2.8%)</strong></td>
<td><strong>8934 (3.6%)</strong></td>
<td><strong>0.79 (0.77 - 0.81)</strong></td>
</tr>
</tbody>
</table>

- **99% or 95% CI**
- Statin better
- Control better
The Big Questions…

% Patients with CHD Event

LDL-C achieved mg/dL

Primary prevention trials
Secondary prevention trials
HPS

CARE-Rx
4S-Rx
LIPID-PL
POSCH-PAP
4S-PL
LRC-PL
WOSCOPS-PL
WOSCOPS
AFCAPS-PL
AFCAPS
ASCOT-Rx
ASCOT-PL
HPS-Rx
LIPID-Rx
POSCH-Rx
TNT-0A
TNT-80A
Prove-IT TIMI 22 – 80A

PL = placebo
Rx = active treatment

Some Answers...

IMPROVE-IT Trial

Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125 mg/dL (or 50–100 mg/dL if prior lipid-lowering Rx)

N=18,144

Standard Medical & Intervventional Therapy

Simvastatin
40 mg

Ezetimibe / Simvastatin
10 / 40 mg

Duration: Median 6 years follow-up (5314 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156.826-32; Califf RM NEJM 2009;361.712-7; Blazing MA AHJ 2014;168:205-12
Some Answers...

IMPROVE-IT Trial
Some Answers...

IMPROVE-IT Trial

Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

Event Rate (%) vs Time since randomization (years)

- HR 0.936 CI (0.887, 0.988)
- p=0.016

6.4% Relative Treatment effect

2.0% Absolute Treatment difference

NNT = 50

7-year event rates

Cannon CP, NEJM 2015;372:2387-97
Monoclonal Antibody Against PCSK9 Blocks The PCSK9/LDL-R Interaction

GLAGOV Trial

Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound

- Prior intravascular ultrasound (IVUS) trials have shown that statins slow progression or induce regression of coronary disease in proportion to the magnitude of LDL-C reduction.

- No other LDL-lowering therapy has shown regression in an IVUS trial.

- GLAGOV examines whether the addition of evolocumab, to a background of statin therapy, can reduce the burden of atherosclerosis as assessed by IVUS.

GLAGOV Trial: Study Design

- 968 patients at 197 global centers with symptomatic CAD and other high risk features and coronary angiography showing 20-50% stenosis in a target vessel.

  - Stable, optimized statin dose for 4 weeks with LDL-C >80 mg/dL or 60-80 mg with additional high risk features.

  - Intravascular ultrasound via motorized pullback at 0.5 mm/sec through >40 mm segment.

- 423 statin completers

  - Statin monotherapy
  
  - 61 patients did not complete
  
  - 423 statin completers

- 423 evolocumab completers

  - Statin plus monthly SC evolocumab 420 mg
  
  - 61 patients did not complete

Follow-up IVUS of originally imaged “target” vessel (n=846)

**GLAGOV Trial: LDL-C Effect**

Mean LDL-C 93.0 mg/dL
Change from baseline 3.9%

Mean LDL-C 36.6 mg/dL
Change from baseline -59.8%

GLAGOV Trial: Primary Endpoint

Change in Percent Atheroma Volume (%)

<table>
<thead>
<tr>
<th></th>
<th>Statin monotherapy</th>
<th>Statin-evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>-0.2</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>-0.4</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>-0.6</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>-0.8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>-1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GLAGOV Trial: Achieved LDL and Plaque Regression

FOURIER Trial: Study Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

Evolocumab
140 mg Q2W or 420 mg QM

RANDOMIZED
DOUBLE BLIND

Placebo
Q2W or QM

Follow-up Q 12 weeks

FOURIER: LDL-C Reductions

Placebo

59% mean reduction (95%CI 58-60), P<0.00001

Absolute reduction: 56 mg/dl (95%CI 55-57)

Evolocumab

(median 30 mg/dl, IQR 19-46 mg/dl)

Sabatine MS et al. NEJM 2017;177.
FOURIER Trial: Clinical Outcomes

Hazard ratio 0.80
(95% CI, 0.73-0.88)
P<0.00001

Placebo
9.9%
7.9%

Evolocumab
0%
1%
2%
3%
4%
5%
6%
7%
8%
9%
10%

CV Death, MI, or Stroke

0 6 12 18 24 30 36
Months from Randomization

Sabatine MS et al. NEJM 2017;177.
ODYSSEY Outcomes: Study Design

- Post-ACS patients (1 to 12 months)
  - Run-in period of 2–16 weeks on high-intensity or maximum-tolerated dose of atorvastatin or rosuvastatin
  - At least one lipid entry criterion met

Randomization

Alirocumab SC Q2W

Placebo SC Q2W

Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose
ODYSSEY Outcomes: Clinical Outcomes

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

ODYSSEY Outcomes: Clinical Outcomes

ODYSSEY Outcomes: Clinical Outcomes

HR 0.85 (95% CI 0.78, 0.93); P=0.0003

Number at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Number at Risk</th>
<th>Years Since Randomization</th>
<th>Placebo</th>
<th>Alirocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9482</td>
<td>0</td>
<td>8805</td>
<td>8846</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>9482</td>
<td>1</td>
<td>8201</td>
<td>8345</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>3471</td>
<td>3574</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td>629</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td></td>
<td>653</td>
</tr>
</tbody>
</table>

Schwartz, GC et al. NEJM 2018; Nov. 29 [Epub ahead of print]
Putting It All Together

FOURIER Trial: Achieved LDL-C

LDL-C (mg/dL) at 4 wks
- ≥100
- 70-99
- 50-69
- 20-49
- <20

Adj RRR
Ref.
- ↓10%
- ↓13%
- ↓25%
- ↓31%

Kaplan-Meier Event Rate

Months after Randomization

Evolving Paradigm of LDL-C Management

High is bad
Average is not good
Lower is better
Even lower is even better
Lowest is best
They Knew It All Along...

A Receptor-Mediated Pathway for Cholesterol Homeostasis

MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

The LDL-receptor studies lend experimental support to the epidemiologists’ suggestion that the levels of plasma cholesterol usually seen in Western industrialized societies are inappropriately high (9). This support derives from knowledge of the affinity of the LDL receptor for LDL. The receptor binds LDL optimally when the lipoprotein is present at a cholesterol concentration of 2.5 mg/dl (28). In view of the 10-to-1 gradient between concentrations of LDL in plasma and interstitial fluid, a level of LDL-cholesterol in plasma of 25 mg/dl would be sufficient to nourish body cells with cholesterol (118). This is roughly one-fifth of the level usually seen in Western societies (Fig. 16) (119). Several lines of evidence suggest that plasma levels of LDL-cholesterol in the range of 25 to 60 mg/dl (total plasma cholesterol of 110 to 150 mg/dl) might indeed be physiologic for human beings.

Evolving Paradigm of LDL-C Management

Historical Perspective of LDL-C Targets/Thresholds as Recommended by Globally Recognized Guidelines¹⁻¹³

- **NCEP ATP¹⁻³**
- **AACE/ACE (extreme* ASCVD risk)⁴**
- **AHA/ACC⁵⁻⁶**
- **ESC/EAS (very high CV risk)⁶⁻⁸**
- **ESC/EAS (high CV risk)⁹⁻¹¹**
- **AACE (very high CV risk)¹²**
- **NLA (very high risk)¹³**

*Progressive ASCVD, including UA that persists after achieving an LDL-C < 70 mg/dL (1.8 mmol/L), or established clinical ASCVD in individuals with diabetes, CKD stage 3 or 4, and/or HeFH, or in individuals with a history of premature ASCVD (< 55 years of age for males or < 65 years of age for females), in very high risk ASCVD,* use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider the addition of nonstatins to statin therapy. A threshold is the point/trigger at which intensification of therapy may be considered. Additional AHA/ACC guidelines were published in 2013 but did not provide a recommendation for target LDL-C levels to reduce the ASCVD risk.¹⁰


2018 ACC/AHA Lipid Guidelines
# Table 4. Very High-Risk* of Future ASCVD Events

<table>
<thead>
<tr>
<th>Major ASCVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent ACS (within the past 12 mo)</td>
</tr>
<tr>
<td>History of MI (other than recent ACS event listed above)</td>
</tr>
<tr>
<td>History of ischemic stroke</td>
</tr>
<tr>
<td>Symptomatic peripheral arterial disease (history of claudication with ABI &lt;0.85, or previous revascularization or amputation)</td>
</tr>
</tbody>
</table>
2018 ACC/AHA Guidelines

Table 4. Very High-Risk* of Future ASCVD Events

<table>
<thead>
<tr>
<th>High-Risk Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</td>
</tr>
<tr>
<td>Heterozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>CKD (eGFR 15-59 mL/min/1.73 m²)</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe</td>
</tr>
<tr>
<td>History of congestive HF</td>
</tr>
</tbody>
</table>
Summary and Conclusions

- Reducing LDL-C with statin therapy is the cornerstone of hyperlipidemia management.
- It is important to start early to prevent heart disease and critical to aggressively lower LDL-C to prevent any further events.
- Clinical trials of ezetimibe and PCSK9 inhibitors have demonstrated additional reductions in adverse events with additional reductions in LDL-C.
- The ACC/AHA guidelines recommend additional lipid lowering therapy in patients with very high risk ASCVD who have LDL > 70mg/dL.
Beyond the Numbers:
The Benefits of Early and Aggressive Lowering of LDL Cholesterol

Nihar R. Desai, MD, MPH
Associate Professor of Medicine, Yale School of Medicine
Associate Chief, Section of Cardiovascular Medicine
Investigator, Center for Outcomes Research and Evaluation
Join us for the next session of the series:
**Understanding and Interpreting Your Cholesterol Blood Test**
June 23, 2020 at 5:00 PM ET

Presenter: Joseph DeBoe, DNP
Moderator: Andrea Baer, MS, BCPA