Cholesterol Management: Newer Recommendations and Therapies

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Disclosures

Dr. Wong receives research support through his institution from Novartis, Regeneron, Novo Nordisk, and Lilly and is a consultant for Novartis, Agepha, Ionis, and Kaneka
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What Is Desirable Cholesterol?

Cholesterol Levels Among Different Human Populations

- **Hazda**: Mean total cholesterol, 80-110 mg/dL (2.0-2.9 mmol/l)
- **Inuit**: Mean total cholesterol, 90-120 mg/dL (2.3-3.1 mmol/l)
- **!Kung**: Mean total cholesterol, 90-120 mg/dL (2.3-3.1 mmol/l)
- **Pygmy**: Mean total cholesterol, 90-120 mg/dL (2.3-3.1 mmol/l)
- **San**: Mean total cholesterol, 100-130 mg/dL (2.6-3.4 mmol/l)
- **Adult American**: Mean total cholesterol, 120-160 mg/dL (3.1-4.1 mmol/l)

Hunter-gatherer humans
- Mean total cholesterol: (100-150 mg/dL) (2.6-3.9 mmol/l)

Human neonates:
- LDL-C: 0.8-1.9 mmol/l
- Mean total cholesterol: (30-75 mg/dL)

Evolution of LDL-C Targets with Newer Guidelines

- **ATP I (1988)**: LDL< 130mg/dl, HRG
- **ATP II (1993)**: LDL< 100mg/dl, CAD
- **ATP III (2001)**: LDL< 100mg/dl, CAD & CAD EQ
- **ATP III (Update 2004)**: LDL< 70mg/dl, VHRG
- **ACC/AHA (2006)**: LDL< 70mg/dl, VHRG
- **ADA/ACC 2008**: LDL< 70mg/dl, CAD
- **EAS 2011**: LDL< 70mg/dl, CAD
- **ACC/AHA 2013**: No LDL-C Target
- **ESC / EAS 2016**: LDL<70 mg/dl, CAD
- **ACC/AHA/Multisociety 2018**: LDL>=70 threshold for nonstatins, ASCVD
- **ESC/ EAS 2019**: LDL<55 mg/dl, all ASCVD and very high risk
  - LDL<40, recurrent CAD
- **Lipid Association of India 2020**: LDL<30 mg/dl, extreme risk ASCVD group
- **ACC Evidenced Based Consensus Document 2022**: LDL-C threshold of >=55 mg/dL for non-statin therapy in very high risk ASCVD patients
Evidence-Based Cardioprotective Dietary Patterns

DASH and Mediterranean-style dietary patterns

**High intake of**
- Plant-based foods: vegetables, fruits, and whole grain foods; legumes, nuts, and seeds
- Fish or seafood, lean meats, and non-fat or low-fat (1%) dairy products
- Plant-based oils (non-tropical) in place of animal fats

**Limit intake of**
- High-fat red meat and high-fat dairy products
- Sweets, sugar-sweetened beverages

### Recommendations for Exercise and Physical Activity

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>1. Adults should be routinely counseled in healthcare visits to optimize a physically active lifestyle.</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>2. Adults should engage in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to reduce ASCVD risk.</td>
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</tbody>
</table>
# Intensity of Statin Therapy

## High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40†)-80 mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong></td>
<td><strong>Simvastatin 10 mg</strong></td>
</tr>
<tr>
<td><strong>Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Rosuvastatin (5) 10 mg</strong></td>
<td><strong>Pravastatin 10-20 mg</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Lovastatin 20 mg</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Fluvastatin 40 mg</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Fluvastatin XL 80 mg</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Fluvastatin 40 mg bid</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Pitavastatin 2-4 mg</strong></td>
</tr>
</tbody>
</table>

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.
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 $\geq 160$ mg/dL ($\geq 4.1$ mmol/L)

- **Age 40-75 y and LDL-C $\geq 70$-190 mg/dL ($\geq 1.8$-$4.9$ mmol/L)**
  - 10-year ASCVD risk percent begins risk discussion
  - 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 $\geq 160$ mg/dL ($\geq 4.1$ 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 ($\geq 175$ mg/dL, $\geq 2.0$ mmol/L)

**Risk discussion:**
- If risk factors present then risk discussion regarding moderate-intensity statin therapy (Class IIb)
- Risk discussion: If risk enhancers present favor statin, initiate moderate-intensity statin to reduce LDL-C by 30%-49% (Class I)
- Risk discussion: Initiate statin to reduce LDL-C $\geq 50$% (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 $\geq 75$th percentile, initiate statin therapy
Recommendations for Primary Prevention Patients without Diabetes or LDL-C ≥190 mg/dL

- Consider moderate intensity statin therapy for those at 5-<20% 10-year ASCVD risk.
- If 30-49% LDL-reduction and LDL-C<100 not reached, consider high intensity statin.
- For high risk (≥20%) persons, consider high intensity statin.
- If ≥50% LDL-C reduction and LDL-C<70 mg/dL not reached, consider adding ezetimibe.
- Address HTG according to 2021 ACC ECDP on HTG.
Recommendations for Patients with Diabetes without ASCVD

- All pts at least on moderate intensity statin
- If 10-year risk >=7.5% or DM risk enhancers or subclinical athero present, then give high intensity statin
- For those with >=20% risk, of >=50% LDL-C reduction or LDL-C<70 not reached, consider adding ezetimibe
- Address HTG based on 2021 ACC ECDP on HTG
**Very High-Risk* of Future ASCVD Events**

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

<table>
<thead>
<tr>
<th>High-Risk Conditions</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</td>
<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>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
<td>CKD (eGFR 15-59 mL/min/1.73 m²)</td>
</tr>
<tr>
<td>Current smoking</td>
<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>
<td></td>
</tr>
</tbody>
</table>

* Very High-Risk is defined as multiple major ASCVD events or one major ASCVD event and multiple high risk conditions
Recommendations for ASCVD Very High Risk Patients

If LDL-C >55 mg/dL (or non-HDL-C >85 mg/dL) despite high intensity or maximally tolerated statin

- Ezetimibe or a PCSK9 inhibitor are the first choice of non-statins for further LDL-C lowering which have been shown to improve ASCVD outcomes
- Inclisiran or bempedoic are alternative non-statin therapies that may be considered
Recommendations for ASCVD Not at Very High Risk Patients

If LDL-C >70 mg/dL (or non-HDL-C >100 mg/dL) despite high intensity or maximally tolerated statin

- Ezetimibe or a PCSK9 inhibitor are the first choice of non-statins for further LDL-C lowering which have been shown to improve ASCVD outcomes
- Inclisiran or bempedoic are alternative non-statin therapies that may be considered
Despite ASCVD Benefit with Statin Monotherapy, Substantial Residual CV Risk Remains

CHD events occur in patients treated with statins

![Bar chart showing CHD events in patients treated with statins](chart.png)

Residual CV risk may be due not only to other lipid measures that may not be controlled, but other risk factors at suboptimal control such as hypertension, diabetes, or smoking.
Primary Endpoint — ITT

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

HR 0.936 CI (0.887, 0.988)  
p = 0.016

Simva — 34.7%  
2742 events

EZ/Simva — 32.7%  
2572 events

NNT = 50

6% relative risk reduction, but 2% absolute risk reduction

7-year event rates
Impact of an PCSK9 mAb on LDL Receptor Expression
LDL Cholesterol

**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)
Event rates of 11.3% placebo and 9.8% evolocumab at 2.2 years for absolute risk reduction of 1.5% (NNT 67)
Incremental benefit for reduction of primary endpoint according to achieved LDL-C levels at 4 weeks

<table>
<thead>
<tr>
<th>Achieved LDL-C</th>
<th>Percentage of patients</th>
<th>Evolocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 70 mg/dL</td>
<td>87%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>≤ 40 mg/dL</td>
<td>67%</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>≤ 25 mg/dL</td>
<td>42%</td>
<td>&lt; 0.1%</td>
<td></td>
</tr>
<tr>
<td>≤ 15 mg/dL</td>
<td>5%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>≤ 10 mg/dL</td>
<td>2%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

![Graph A](image)

- 59% mean reduction (95% CI 58-60), P<0.00001
- Absolute reduction: 56 mg/dL (95% CI 55-57)

![Graph B](image)

- Evolocumab (median 30 mg/dL, IQR 19-46 mg/dL)

<table>
<thead>
<tr>
<th>Achieved LDL-C</th>
<th>Hazard ratio (95% CI)</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmol/L</td>
<td>mg/dl</td>
<td></td>
</tr>
<tr>
<td>&lt;0.26</td>
<td>&lt;10</td>
<td>0.69 (0.49-0.97)</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>&lt;20</td>
<td>0.76 (0.64-0.90)</td>
</tr>
<tr>
<td>0.5-1.3</td>
<td>20-49</td>
<td>0.85 (0.76-0.96)</td>
</tr>
<tr>
<td>1.3-1.8</td>
<td>50-69</td>
<td>0.94 (0.82-1.09)</td>
</tr>
<tr>
<td>1.8-2.6</td>
<td>70-99</td>
<td>0.97 (0.86-1.09)</td>
</tr>
<tr>
<td>≥2.6</td>
<td>≥100</td>
<td>Reference</td>
</tr>
</tbody>
</table>

![Graph C](image)

- Adjusted Event Rate (probability)
- P = 0.0012

![Graph D](image)

- Achieved LDL-C levels in mmol/L
- Reference
GLAGOV Study of Evolocumab: Mean On-Treatment LDL-C vs. Change in PAV

Locally Weighted Polynomial Regression (LOESS) Plot with 95% confidence limits

Nissen et al., JAMA 2017
Bempedoic Acid and Bempedoic Acid-Ezebimibe FDA-Approved February 2020

Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C. The effect of on cardiovascular morbidity and mortality has not been determined. First oral, once-daily, non-statin LDL-C lowering medicine approved since 2002 for indicated patients.
CLEAR HARMONY trial reported at ESC showed in 2000+ pts on maximially tolerated statin therapy placebo corrected LDL-C reduction of 16.8% in treated group.

Bempedoic Acid – Ezetimibe fixed dose combination provides 36% LDL-C lowering

Bempedoic acid trials showed no safety concerns.
CLEAR Outcomes Trial (N=14,032)

- Age 18 - 85 years
- History of ASCVD (CAD, symptomatic PAD, CVD disease, or at high risk for a CV event)
- Statin intolerance (intolerant ≥2 statins, one at low dose)
- LDL ≥ 100 mg/dL

Exclusion criteria:
- Fasting TGs >500 mg/dL
- Major CV events, TIA, or unstable or symptomatic arrhythmia < 90 days
- History of severe HF
- Uncontrolled HTN or DM

Randomized 1:1 Double Blinded

Bempedoic acid 180 mg po QD (N ≈ 7000)

Placebo po QD (N ≈ 7000)

Estimated average treatment duration: 3.75 years

CV death, nonfatal MI, nonfatal stroke, or coronary revascularization.

Start: November 18, 2016
Enrollment end: Sep 5, 2019
Completion: Q4 of 2022

Nissen S et al., NEJM 2022
CLEAR OUTCOMES (RESULTS)

A Four-Component MACE (Primary End Point)

- Hazard ratio, 0.87 (95% CI, 0.79–0.96)
- P=0.004

B Three-Component MACE

- Hazard ratio, 0.85 (95% CI, 0.76–0.96)
- P=0.006

Nissen S et al., NEJM 2022
**QUESTION** In statin-intolerant primary prevention patients at high cardiovascular risk, does bempedoic acid reduce major adverse cardiovascular events?

**CONCLUSION** Treatment with bempedoic acid in primary prevention patients has the potential to reduce major adverse cardiovascular events.

**POPULATION**
- 2481 Women
- 1725 Men

Statin-intolerant adults without a prior cardiovascular event

Mean age: 68 years

**LOCATIONS**
- 1250 Centers worldwide

**INTERVENTION**
- **Bempedoic acid**
  - 180-mg oral dose administered daily
  - 2100 patients randomized

- **Placebo**
  - Matching placebo
  - 2106 patients randomized

**FINDINGS**
- Composite end point occurrence
  - **Bempedoic acid** 5.3% (111 of 2100 patients)
  - **Placebo** 7.6% (161 of 2106 patients)

**PRIMARY OUTCOME**
- Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization

Risk reduction was significant:
- Adjusted hazard ratio, 0.70 (95% CI, 0.55-0.89); P=.002

INCLISIRAN – FDA Approved Dec. 2021 for ASCVD and HeFH Patients Needing Additional LDL-C Lowering

Background and rationale
Harnessing the natural process of RNAi

Small interfering double-stranded RNA
- Harnesses the natural process of RNAi
- Nucleotides modified for durability and low immunogenicity
- Distributed to liver due to GalNAc conjugation
- Inhibits production of PCSK9 specifically, durably and potently
ORION-11: Efficacy
Durable, potent and consistent effect over 18 months

- Percent change in LDL-C over time – observed values ITT patients

P-value for placebo – inclisiran comparison at each time point <0.00001
Inclisiran and cardiovascular events: a patient-level analysis of phase III trials

Kausik K. Ray, Wolfgang Koenig, Gregory G. Schwartz, Lorena Garcia Conde

Epidemiology and prevention

Inclisiran and risk of reported MACE from the patient-level pooled ORION-9, ORION-10 and ORION-11 trials.

AE, adverse event; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; mRNA, messenger ribonucleic acid; OR, odds ratio; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering ribonucleic acid.

Keywords: Inclisiran, LDL-C, Major adverse cardiovascular events, Atherosclerotic cardiovascular disease
FH is more common than many well known genetic diseases but <10% are diagnosed – key challenge is to improve identification

- 1:250-300 worldwide with HeFH, about 1:500,000 with HoFH
- Autosomal dominant
- Approx 1M FH patients in US, <10% diagnosed
- 20 fold increased risk of coronary heart disease for HoFH
- Causes 20% of MIs before age 45 and 5% before age 60

Hopkins et al. J. Clinical Lipidology. 2011
Goldberg et al. J. Clinical Lipidology. 2011
FH is a “Winnable battle”: Therapeutic Options

Available Therapies

- High intensity statin
- Ezetimibe
- PCSK9mAb (HeFH)
- Bempedoic Acid (HeFH)
- Mipomersen (HoFH)
- Lomitapide (HoFH)
- Evinacumab (HoFH)
- Inclisiran (HeFH)

Emerging Therapies

- Pelacarsen for Lp(a)

Dutch subjects with HeFH on or off statin treatment (Versmissen et al)
Evinacumab, a fully human monoclonal antibody blocks ANGPTL3, reducing LDL-C production independent of the LDL receptor.

47% relative reduction in LDL-C at 24 weeks

(Raal FJ et al. NEJM 2020)
Residual HTG Predicts Residual ASCVD Risk Despite LDL-C at Goal on Statin Monotherapy

Despite achieving LDL-C <70 mg/dL with a high-dose statin, patients with TG ≥150 mg/dL have a 41% higher risk of coronary events*

*Death, myocardial infarction, or recurrent acute coronary syndrome, PROVE-IT-TIMI 22

But prior clinical trials of TG lowering with fibrates (e.g., ACCORD and FIELD) and niacin (e.g., AIM-HIGH, HPS2 Thrive) have not been shown to reduce ASCVD outcomes
There were approximately 12% increases in LDL-C as well as increases in ApoB in the pemafibrate group, which may have counteracted any benefit from lowering TG levels. Pemafibrate was also associated with increased adverse renal events and VTE.
Dubious Content of **Leading US Fish Oil Dietary Supplements**

- Up to 36% of content may be saturated fat
- Omega-3 FA content often overstated
- Oxidation of omega-3 FA content can be high
  - even those meeting industry standards are more oxidized than Rx meds
- Contamination risk (pesticides, PCBs, etc.)
- Difficult to achieve EPA+DHA doses similar to Rx meds

High saturated fatty acid content of common fish oil dietary supplement makes it **solid at room temperature** (post-isolation)

Key Inclusion Criteria

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) or ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*

3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

Adapted with permission* from: Bhatt DL et al. Clin Cardiol. 2017;40:138-48. [*https://creativecommons.org/licenses/by-nc/4.0/]
Primary Endpoint:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Patients with an Event (%)

Years since Randomization

Hazard Ratio 0.75
(95% CI 0.68–0.83)
RRR=24.8%
ARR=4.8%
NNT=21 (95% CI 15–33)
P=0.00000001

**New Guidelines/Recommendations for Icosapent Ethyl to Prevent ASCVD in Patients with TG 135-499 mg/dL**

<table>
<thead>
<tr>
<th>Scientific Society</th>
<th>Treatment with Statin and Icosapent Ethyl for ASCVD Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Diabetes Association (ADA)</td>
<td>In patients with ASCVD or other cardiac risk factors with controlled LDL-C, but elevated triglycerides (135-499)</td>
</tr>
<tr>
<td>European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS)</td>
<td>In high-risk (or above) patients with TG levels between 135-499 mg/dL, n-3 PUFAs (icosapent ethyl 2x2 g/day) should be considered in combination with a statin</td>
</tr>
<tr>
<td>National Lipid Association (NLA)</td>
<td>For patients 45 years of age or older with clinical ASCVD, or 50 years of age or older with diabetes mellitus requiring medication and ≥1 additional risk factor, with fasting TG 135-499 mg/dL</td>
</tr>
<tr>
<td>American Heart Association (AHA)</td>
<td>The use of n-3 FA (4 g/d) for improving atherosclerotic cardiovascular disease risk in patients with hypertriglyceridemia is supported by a 25% reduction in major adverse cardiovascular events in REDUCE-IT</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists (AACE) / American College of Endocrinology (ACE)</td>
<td>If TG 135-499, add icosapent ethyl 4 g/day if high ASCVD risk on maximally tolerated statins</td>
</tr>
</tbody>
</table>

atherosclerotic cardiovascular disease; HTG, hypertriglyceridemia; LDL-C, low-density lipoprotein cholesterol; PUFA, polyunsaturated fatty acids; TG, triglyceride.

Elevated Lp(a) is a critical risk factor for ASCVD

Lp(a) contains all the proatherogenic components of LDL-C plus apo(a).

Elevated Lp(a)
is primarily genetically determined, without significant dietary or environmental influences.

Elevated Lp(a) is an independent, genetic, and causal risk factor for ASCVD.

The Lp(a) particle is composed of 2 parts:
1. LDL-like particles with apoB-100, and
2. apo(a) covalently bound to apoB-100 by disulfide bonds.

apo(a) contains 10 types of KIV subtypes, an inactive protease-like domain, and oxidized phospholipids.


apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; KIV, kringle 4; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); OxPL, oxidized phospholipids; P, protease.

Elevated Lp(a) is an inherited, independent, and causal risk factor for ASCVD\textsuperscript{1,2}

Epidemiological, genome-wide association, and Mendelian randomization studies have demonstrated an association between elevated Lp(a) levels and increased ASCVD risk\textsuperscript{1,2}

people with elevated Lp(a) levels have increased ASCVD risk\textsuperscript{3,*}

- MI\textsuperscript{3-5} 3- to 4-fold risk
- Aortic valve stenosis\textsuperscript{3,5} 3-fold risk
- Ischemic stroke\textsuperscript{3,7} 1.6-fold risk
- Heart failure\textsuperscript{3,8} 1.5- to 2-fold risk
- CV mortality\textsuperscript{3,9} 1.5-fold risk
- All-cause mortality\textsuperscript{3,9} 1.2-fold risk

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; Lp(a), lipoprotein(a); MI, myocardial infarction.

\textsuperscript{*}Data based on population-based studies comparing risk in patients with low Lp(a) levels in each study vs those with higher Lp(a) levels.

\textsuperscript{1}Tsimikas S. J Am Coll Cardiol. 2017;69(6):692-711.


\textsuperscript{5}Kamstrup PR et al. JAMA. 2009;301(22):2331-2339.


\textsuperscript{8}Kamstrup PR, Nordestgaard BG. JACC Heart Fail. 2016;4(1):78-87.

Lp(a) Testing: Unmet Need

- Only 1.2% of SP and 1.3% of PP patients had an Lp(a) test done.
- Among SP patients, adherence to lipid lowering therapies was only slightly greater in those with Lp(a) >175 nmol/L vs. <175 nmol/L (35% vs. 33%)

Lipoprotein(a) Testing Trends in a Large Academic Health System in the United States (Bhatia HS et al., JAHA 2023)
- Evaluation of 5.5 million US adults in the Univ. of CA Health data warehouse in 2017-2021
- Only 18,972 (0.3%) had Lp(a) testing done
- Older persons, men, and those of White race more likely to be tested
- Small increase in testing among those with a CVD diagnosis over recent years
Dyslipidemia management and CVD prevention guidelines recommend considering Lp(a) testing for a variety of patients for ASCVD risk assessment

<table>
<thead>
<tr>
<th>Guidelinesa</th>
<th>At least once in all patients’ lifetimesb</th>
<th>Family history of prematurec ASCVD</th>
<th>Personal history of prematurec ASCVD</th>
<th>Moderate to high ASCVD risk (when further risk stratification would be beneficial)</th>
<th>Refractory elevation of LDL-C despite LDL-C–lowering therapy (statin resistance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACE/ACE (2020)(^1,a)</td>
<td>---</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NLA (2019)(^2,a)</td>
<td>---</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>AHA/ACC (2018/19)(^3,4,a)</td>
<td>---</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CCS (2021)(^5,a)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>ESC/EAS (2016/19)(^6,a)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HEART UK (2019)(^7,a)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CCS, Canadian Cardiovascular Society; CV, cardiovascular; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NLA, National Lipid Association. A green check indicates guidelines recommend considering Lp(a) testing in this setting. *Synopsis of guideline recommendations. **Recommended once in each person’s lifetime in 2019 dyslipidemia guidelines\(^b\) but not in 2016 CVD prevention guidelines. \(^c\)Premature” defined as ASCVD occurring in males aged <55 years or females aged <65 years.\(^1-6\)

RNA Targeted Therapies for Lipoprotein(a) Lowering

Pelacarsen – antisense oligonucleotide (ASO) therapy

Olpasiran – small interfering RNA (siRNA) therapy

N-acetyl-galactosamine (GalNAc) modifications improve hepatocyte targeting
Pelacarsen Phase 2 trial

Mean 80% reduction in Lp(a) with pelacarsen 80 mg/monthly equivalent dose
98% of patients reached ideal level of <50 mg/dL (<125 nmol/L)

Waterfall Plot – individual Lp(a) decreases ranged from 43-100%

Olpasiran: Phase 2 Study

Koren et al Nat Med. 2022;28:96-103
N=213,619 pts with ASCVD
N=116,097 pts with very high risk ASCVD

- 57% had no LDL-C test in past year
- 24% not on lipid therapy
- Among treated, only 52% on high intensity statin
- 52% of those on high intensity statin still with LDL-C >70 mg/dL
IMPROVE ASCVD Quality Improvement Program at UCI Health Launched April 2023 for Patients with ASCVD

- Health Maintenance prompt for lipid profile if not done within past 18 months
- Best practice advisory (BPA) for initiation of high intensity statin if not already on one, or requirement to indicate contraindication (eg statin intolerance, refusal)
- BPA / smart set for consideration of non-statin (including ezetimibe, PCSK9 inhibitor, inclisiran, and bempedoic acid) if on maximially tolerated statin therapy and LDL-C ≥70 mg/dL (or ≥55 mg/dL if very high risk ASCVD)
- Expanded to those with LDL-C ≥190 or FH with Lp(a) testing also added in August 2023
According to guidelines, patients with ASCVD should be on a high intensity statin to reduce their future ASCVD risk unless contraindicated; your patient is not currently on a high intensity statin. Order a high intensity statin and follow-up labs in about 6 weeks or indicate why you are not ordering.

**Recommendation of High Intensity Statin**
**Definition of Statin Intolerance**

<table>
<thead>
<tr>
<th>Order</th>
<th>Do Not Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin (LIPITOR) tablet 40 mg</td>
<td></td>
</tr>
<tr>
<td>atorvastatin (LIPITOR) tablet 80 mg</td>
<td></td>
</tr>
<tr>
<td>rosuvastatin (CRESTOR) tablet 20 mg</td>
<td></td>
</tr>
<tr>
<td>rosuvastatin (CRESTOR) tablet 40 mg</td>
<td></td>
</tr>
<tr>
<td>Lipid Panel</td>
<td></td>
</tr>
<tr>
<td>Comprehensive Metabolic Panel</td>
<td></td>
</tr>
</tbody>
</table>

**Last LDLCALC, Collected: 12/6/2022 2:52 PM = 132 MG/DL**
**Last LDL: Not on file**

**Acknowledge Reason**
- Statin Intolerance
- Contraindicated-Other
- At Highest Tolerated Dose
- Patient refused
- Other - See Comment

[Accept]
UC Irvine ASCVD Very High Risk BPA for Non-Statin Therapy if LDL-C >55 mg/dL despite High Intensity Statin Therapy

Patient is considered ASCVD at very high risk and is on a high intensity or maximally tolerated statin (or statin intolerant), but LDL-C is NOT <55 mg/dL, consider adding ezetimibe or PCSK9 inhibitor

⚠️ Recommendation for Non-Statin Therapy
2022 ACC Expert Consensus Decision Pathway
2018 Guideline on the Management of Blood Cholesterol

Patient is very high risk for recurrent ASCVD event
(Very high ASCVD risk is defined as two (2) or more major ASCVD events or one (1) major ASCVD event and two or more high risk conditions.)

<table>
<thead>
<tr>
<th>Major ASCVD Events</th>
<th>High Risk Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent ACS (past 12 months)</td>
<td>Age &gt;=65</td>
</tr>
<tr>
<td>Hx of MI</td>
<td>Heterozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>Hx of ischemic stroke</td>
<td>Hx of prior CABG or percutaneous coronary intervention</td>
</tr>
<tr>
<td></td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>HTN</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
</tr>
<tr>
<td></td>
<td>Current smoking</td>
</tr>
<tr>
<td></td>
<td>Persistent elevated LDL despite high intensity statin or ezetimibe</td>
</tr>
<tr>
<td></td>
<td>Hx of CHF</td>
</tr>
</tbody>
</table>

Patient's ASCVD Documented Risk Factors: MI in last 12 months (Major Event), Hypertension (1 pt), CHF (1 pt), Last LDL: Not on file, Last LDL CALC, Collected: 1/13/2023 = 65

Open SmartSet  Do Not Open  Additional lipid lowering options including PCSK9 inhibitor, labs, Ref to Card and information to support prescribing best practices Preview

Order  Do Not Order  ezetimibe (ZETIA) tablet 10 mg

Acknowledge Reason
Contraindicated  Patient Refused  Other (see comment)

Accept
A one-time lipoprotein (a) is recommended for your patient, based on one of the following criteria: Personal or family history of ASCVD, diagnosed or suspected familial hypercholesterolemia, any prior LDL >=190 mg/dl, or aortic stenosis.

About Lipoprotein(a) and Recommendations

Order | Do Not Order

Lipoprotein (a), Blood

Acknowledge Reason

Patient Refused | Defer (Address Next Visit)

Lipoprotein(a) is a low density lipoprotein-like particle that is a powerful genetic risk factor for cardiovascular disease, including coronary artery disease, stroke, and aortic valve stenosis. Levels of >=125 nmol/L, or >=50mg/dl, are indicated as a risk enhancing factor for the purposes of initiating or intensifying preventive therapies such as statins.
Top 10 Take Home Messages

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

3. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

4. Use a LDL-C threshold of 70 mg/dL (or non-HDL-C 100 mg/dL) to consider addition of nonstatins to statin therapy. For very high risk ASCVD this LDL-C threshold is 55 mg/dL (non-HDL-C 85 mg/dL)
Top 10

Top 10 Take Home Messages

5. Ezetimibe or a PCSK9i is the first choice for non-statin therapy, followed by inclisiran or bempedoic acid.

6. In patients with severe primary hypercholesterolemia (LDL-C level $\geq 190$ mg/dL [$\geq 4.9$ mmol/L]) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

7. In patients 40 to 75 years of age with diabetes mellitus start moderate intensity statin and if $>7.5\%$ 10-year risk high intensity statin therapy and for those $>20\%$ risk consideration for ezetimibe if LDL-C $< 70$ mg/dL is not achieved.

8. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.
Top 10 Take Home Messages

8. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, for those 10-year ASCVD risk of 5-<20% risk, start a moderate-intensity statin, consider high intensity if 30-49% LDL-C reduction of LDL <100 mg/dl not achieved.

9. In adults 40 to 75 years of age without diabetes mellitus and with >=20% 10-year ASCVD risk consider high intensity statin and if 50% LDL-C reduction or <70 mg/dL not achieved, consider adding ezetimibe.

10. Address hypertriglyceridemia according to 2021 ACC ECDP on hypertriglyceridemia – those with ASCVD or DM and multiple RF maximized on statin therapy, consider icosapent ethyl therapy.
THANK YOU

Preventive Cardiology Program
Take control of your health

Life-threatening cardiac events often can be prevented through early diagnosis, risk assessment, treatment and lifestyle changes.

The UC Irvine Health Preventive Cardiology Program uses the latest evidence-based guidelines for cardiovascular disease prevention. Services include:

- Initial evaluation by cardiologist, plus follow-up to track progress
- Comprehensive laboratory measures for cardiac risk factors and biomarkers, plus further evaluation with optional imaging tests
- Computerized cardiovascular risk profiles and risk scoring
- Comprehensive dietitian consultation with a specific focus on cardiovascular risk factor management
- Physical activity prescriptions and consultations with an exercise specialist
- A full report sent to the patient’s referring physician when the program is finished

Our preventive cardiology program’s multidisciplinary team includes:

- Cardiologists
- Registered dietitian
- Exercise physiologist
- Prevention researchers/specialists

Our program can help you if you have been diagnosed with at least one risk factor for cardiovascular disease, including:

- Hypertension
- Hypercholesterolemia/dyslipidemia
- Metabolic syndrome
- Diabetes
- Cigarette smoking

Patients with pre-existing cardiovascular disease who need more guidance with risk factor modification to prevent disease progression or recurrence are also ideal candidates.

To learn more, call 714-456-6699.

15th Annual Orange County Symposium for Cardiovascular Disease Prevention