GOAL-DIRECTED THERAPY IN LIPID MANAGEMENT

Guidelines / practice

2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

Robert Chilton
Professor of Medicine
University of Texas Health Science Center
Director of Cardiac Catheterization labs
Director of clinical proteomics

JACC 2017;70:1785 guidelines
Which target?

Plaque stabilization

- Acute coronary syndrome
- Unstable plaque in body

Plaque regression

- Regression of atherosclerosis

Lifestyle wins: but no interest
Long term
Multiple plaque ruptures from a patient with left common iliac artery stenosis

N=101

42% of patients with PAD have ruptures

ACS more common in PAD rupture p<0.01)

Male sex more common p<0.01

Circ Cardiovasc Interv. 2010;3:63-70
Statins Have a Dose-Dependent Effect on Amputation and Survival in Peripheral Artery Disease Patients....lower is better for target

155,647 VA patients with incident PAD

<table>
<thead>
<tr>
<th></th>
<th>Mortality HR (95% CI)</th>
<th>Amputation HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-level Propensity Score Matched Analysis (N= 30,780)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propensity Score Matched Model, Crude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet only- No statin</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Low-Moderate intensity statin</td>
<td>0.83 (0.79 , 0.88)</td>
<td>0.84 (0.75 , 0.93)</td>
</tr>
<tr>
<td>High intensity statin</td>
<td>0.72 (0.68 , 0.76)</td>
<td>0.69 (0.61 , 0.76)</td>
</tr>
<tr>
<td>Propensity Score Matched Model, Adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet only- No statin</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Low-Moderate intensity statin</td>
<td>0.80 (0.75 , 0.85)</td>
<td>0.80 (0.70 , 0.91)</td>
</tr>
<tr>
<td>High intensity statin</td>
<td>0.70 (0.66 , 0.75)</td>
<td>0.60 (0.52 , 0.69)</td>
</tr>
<tr>
<td><strong>2-level propensity matched analysis (N=30,418)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propensity Score Matched Model, Crude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-Moderate intensity statin</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>High intensity statin</td>
<td>0.86 (0.82 , 0.91)</td>
<td>0.82 (0.74 , 0.90)</td>
</tr>
<tr>
<td>Propensity Score Matched Model, Adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-Moderate intensity statin</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>High intensity statin</td>
<td>0.85 (0.80 , 0.90)</td>
<td>0.78 (0.68 , 0.89)</td>
</tr>
</tbody>
</table>

High intensity statins decrease risk of amputation and death in PAD patients

10.1161/CIRCULATIONAHA.117.032361
### Mortality HR and 95\% Confidence Intervals

<table>
<thead>
<tr>
<th>Group</th>
<th>Low-Medium vs. None (HR, 95% CI)</th>
<th>High vs. None (HR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N=90,257)</td>
<td>0.84 (0.82, 0.86)</td>
<td>0.73 (0.70, 0.76)</td>
</tr>
<tr>
<td>&lt;75 years (N=71,327)</td>
<td>0.84 (0.82, 0.87)</td>
<td>0.73 (0.70, 0.76)</td>
</tr>
<tr>
<td>&gt;=75 years (N=18,930)</td>
<td>0.85 (0.82, 0.89)</td>
<td>0.75 (0.69, 0.81)</td>
</tr>
<tr>
<td>Male (N=88,458)</td>
<td>0.84 (0.82, 0.86)</td>
<td>0.73 (0.70, 0.76)</td>
</tr>
<tr>
<td>Female (N=1,799)</td>
<td>0.99 (0.80, 1.23)</td>
<td>0.72 (0.53, 0.98)</td>
</tr>
<tr>
<td>DM (N=41,652)</td>
<td>0.84 (0.81, 0.87)</td>
<td>0.76 (0.72, 0.80)</td>
</tr>
<tr>
<td>No DM (N=48,605)</td>
<td>0.85 (0.82, 0.88)</td>
<td>0.68 (0.64, 0.73)</td>
</tr>
<tr>
<td>CAD (N=42,743)</td>
<td>0.85 (0.82, 0.88)</td>
<td>0.73 (0.70, 0.77)</td>
</tr>
<tr>
<td>No CAD (N=47,514)</td>
<td>0.84 (0.81, 0.86)</td>
<td>0.72 (0.67, 0.77)</td>
</tr>
<tr>
<td>Whites (N=74,883)</td>
<td>0.85 (0.82, 0.87)</td>
<td>0.73 (0.70, 0.77)</td>
</tr>
<tr>
<td>Blacks (N=14,279)</td>
<td>0.82 (0.77, 0.87)</td>
<td>0.73 (0.66, 0.80)</td>
</tr>
</tbody>
</table>

Decreased Mortality ← → Increased Mortality

American Heart Association

[Graph showing HR and confidence intervals for different groups]
Cardiovascular events: MACE
Long term benefits of keeping LDL low

CHD mortality

Over entire period 27% risk reduction
P<0.001

Percentage with event

Placebo
Pravastatin

Years since randomisation
0 2 4 6 8 10 12 14 16 18 20 22

55 65 75 y
Average age of cohort

All-cause mortality

Over entire period 13% risk reduction
P<0.001

Percentage with event

Placebo
Pravastatin

Years since randomisation
0 2 4 6 8 10 12 14 16 18 20 22

Circulation. (2016); 133:1073-80

WOSCOPS 20-year follow up
Lower LDL less major vascular events

“target lower is better”

372:2387-97

CTTC Lancet (2005) 367;1267-78
CTTC regression

1 mmol/l drop in LDLc = 22% risk reduction

Absolute CV risk

% with CV event

40 80 120 160 mg/dl

LDL

1.3 1.7 3.3 4.1 mmol/l

Higher risk greater benefit

CTTC Lancet (2005) 367;1267-78

Real-world usage

IMPROVE-IT
E-Erosion

White thrombus overlying an intact plaque

G-Culprit plaque rupture

Culprit plaque shows fibrous cap discontinuity with cavity formation

JAMA Cardiol. 2018;3(3):207-214
Simvastatin treatment in rats accelerates re-endothelialization of the mechanically injured artery, in part as a result of increased mobilization of bone marrow-derived endothelial progenitor cells.

**TRANSLATIONAL BIOLOGY**

<table>
<thead>
<tr>
<th></th>
<th>Plaque rupture</th>
<th>Macrophages</th>
<th>Microvessels</th>
<th>Spotty calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosion</td>
<td>0</td>
<td>29%</td>
<td>21%</td>
<td>5%</td>
</tr>
<tr>
<td>Rupture</td>
<td>8%</td>
<td>53%</td>
<td>42%</td>
<td>22%</td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>0.01</td>
<td>0.003</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Rupture: More macrophages and microvessels—Inflammation/Instability

Plaque rupture have elevated levels of systemic matrix metalloproteinase–9 from macrophages and foam cells, indicating active proinflammatory response and degradation of extracellular matrix leading to plaque instability.

*JAMA Cardiol. 2018;3(3):207-214*
Detachment of endothelial cells and exposure of collagen initiate platelet activation and aggregation as well as recruitment of polymorphonuclear leucocytes.

Recruited neutrophils mediate the formation of neutrophil extracellular traps and amplification of thrombosis and local inflammation.

Neutrophils accumulate abundantly in eroded culprit plaques and elevated levels of markers of neutrophil extracellular trap formation are associated with this plaque morphology.

OCT study demonstrated the association between the presence of plaque erosion and elevated levels of serum myeloperoxidase, a marker of neutrophil activation.

These data imply that local endothelial damage rather than widespread coronary arterial inflammation initiates ACS owing to plaque erosion.
Lower the LDL the less plaque volume: less events

Do statins really change the cap thickness in real patients?

1. Yes
2. No

Follow-up - median interval of 9 months

LDL 134 to 89 mg/dl on FU-statin

LDL 122 to 121 mg/dl on diet

JACC imag 2012;5:169-77
Newer trials
FOURIER
FURTHER CARDIOVASCULAR OUTCOMES RESEARCH WITH PCSK9 INHIBITION IN SUBJECTS WITH ELEVATED RISK

MS Sabatine, RP Giugliano, AC Kech, N Honarpour, SM Wasserman, PS Sever, and TR Pedersen, for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017
**BACKGROUND**

**Proprotein convertase subtilisin/kexin type 9 (PCSK9)**

- Chaperones LDL-R to destruction → ↑ circulating LDL-C
- Loss-of-fxn genetic variants → ↑ LDL-R → ↓ LDL-C & ↓ risk of MI

**Evolocumab**

- Fully human anti-PCSK9 mAb
- ~60% ↓ LDL-C
- Safe & well-tolerated in Ph 2 & 3 studies
- Exploratory data suggested ↓ CV events

Sever P & Mackay J. *Br J Cardiol* 2014;21:91-3
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 → RANDOMIZED DOUBLE BLIND Evolocumab SC 140 mg Q2W or 420 mg QM → Follow-up Q 12 weeks → Placebo SC Q2W or QM

**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)
Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001
## CV OUTCOMES

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to acute MI</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>Death due to stroke</td>
<td>0.26</td>
<td>0.32</td>
<td>0.84 (0.49-1.42)</td>
</tr>
<tr>
<td>Other CV death</td>
<td>0.29</td>
<td>0.30</td>
<td>0.94 (0.58-1.54)</td>
</tr>
<tr>
<td>MI</td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
</tbody>
</table>
### DIABETES: CV INDIVIDUAL OUTCOMES

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Diabetes-EvoMab</th>
<th>DM-Placebo</th>
<th>HR (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>3.6%</td>
<td>3.5%</td>
<td>1.05(0.83-1.34)</td>
</tr>
<tr>
<td>MI</td>
<td>5.5</td>
<td>7.5</td>
<td>0.77(0.65-0.92)</td>
</tr>
<tr>
<td>Stroke (diabetes only)</td>
<td>2.9</td>
<td>3.2</td>
<td>0.79(0.62-1.01)</td>
</tr>
<tr>
<td>Coronary revasc</td>
<td>7.4</td>
<td>10</td>
<td>0.77(0.66-0.88)</td>
</tr>
</tbody>
</table>

**After 1st Year: 25% RRR**

HR 0.75 (95%CI 0.63-0.89)

CV death  
MI  
Stroke

EASD: September 15, 2017
GLAGOV

968 high risk patients with symptomatic CAD and 20-50% stenosis by invasive coronary angiography 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 at baseline

Statin Monotherapy (n=484) 18 months treatment Statin plus evolocumab 420 mg QM (n=484)

423 statin completers 423 evolocumab completers

Follow-up IVUS of originally imaged "target" vessel (n=846)
Atheroma Regression

Primary Endpoint:
Percent Atheroma Volume

Mean On-Treatment LDL-C vs. Change in PAV

Regression
<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors(^a)/10-year risk(^b)</th>
<th>Treatment goals</th>
</tr>
</thead>
</table>
| Extreme risk   | – Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL  
– Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH  
– History of premature ASCVD (<55 male, <65 female)                                                                                                                                                                                                                                                                                                                                                   | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
|                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <55            | <80             | <70            |
| Very high risk | – Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%  
– Diabetes or CKD 3/4 with 1 or more risk factor(s)  
– HeFH                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
|                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <70            | <100            | <80            |
| High risk      | – ≥2 risk factors and 10-year risk 10-20%  
– Diabetes or CKD 3/4 with no other risk factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
|                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <100           | <130            | <90            |
| Moderate risk  | ≤2 risk factors and 10-year risk <10%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
|                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <100           | <130            | <90            |
| Low risk       | 0 risk factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
|                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <130           | <160            | NR             |
EFFECT OF NATIVE AND OXIDIZED LOW-DENSITY LIPOPROTEIN ON ENDOTHelial NITRIC OXIDE

- Direct assessment by microsensor
- Bovine EC
- Exposed 1 hr to ↑ LDL

10,001 patients
Stable CAD
Baseline LDL<130 mg/dl

A-80

1° EP↓ CV Death/CVA

Humans-TNT...77 LDL

Circulation March 21, 2000;101:1261-1266
Goal directed yes....lower is better...55 looks good LDL

Safety of drugs treatment

Plaque regression
IVUS: lower is better

Plaque stabilization
Lower is better from trials
Thank you
Selective insulin resistance in liver of mice with type 2 diabetes. Insulin fails to decrease gluconeogenesis, but it continues to stimulate synthesis of fatty acids and Tg. This produces the deadly combination of hyperglycemia and hypertriglyceridemia.
PRIMING VASCULAR ENDOTHELIAL CELLS FOR ENHANCED INFLAMMATORY RESPONSE

- TGRL alone no inflammation in HAEC
- TGRL enhanced inflammatory response 10x to cytokine stimulation

HAECs were repetitively incubated with dietary levels of freshly isolated TGRL for 2 hours per day for 1 to 3 days to mimic postprandial lipidemia.

Ting et al. Circ Res Feb 2007;100:000
Patients who require <25% additional lowering of LDL-C, patients with recent ACS <3 months

Cost considerations with recent availability of generic ezetimibe and future cost savings, ease of use as oral agent with low pill burden, patient preferences, heart failure, hypertension, age >75 years, diabetes, stroke, CABG, PAD, eGFR <60 ml/min/1.73 m2, and smoking.

JACC 2017;70:1785 guidelines
US GUIDELINES-2017 (NON STATIN OR ADDITIONAL LOWERING)

**PCSK-9 inhibitor**

Clinical ASCVD and comorbidities require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin agent.

The clinician–patient discussion should consider the extent of available scientific evidence for net ASCVD risk-reduction benefit, cost, administration by subcutaneous injection, every 14-day or monthly dosing schedule, and storage requirements (refrigeration).

JACC 2017;70:1785 guidelines
ADULTS >21 YEARS OF AGE WITH CLINICAL ASCVD, ON STATIN FOR SECONDARY PREVENTION

- Diabetes,
- Recent (<3 months) ASCVD event
- ASCVD event while already taking a statin
- Poorly controlled other major ASCVD risk factors
- Elevated Lp(a), CKD, symptomatic heart failure

• **Stable ASCVD**

  - Baseline LDL-C >190 mg/dL not due to secondary causes
  - Hemodialysis
  - Prior MI, stroke, CABG
  - Currently smoking
  - Symptomatic PAD

- **None of these**

  - Cath >40% stenosis in >2 vessels
  - HDL <40
  - hsCRP >2
  - Metabolic syndrome
These patients should be treated first with maximally tolerated statin intensity.

If patients have a >50% reduction in LDL-C from baseline (and may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL)

Continue the statin therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

Patients who are unable to tolerate even a moderate-intensity statin should be evaluated for statin intolerance and considered for referral to a lipid specialist.
Patients with stable clinical ASCVD without comorbidities,* on statin for secondary prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†

YES

NO

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.‡ Consider referral to lipid specialist if statin intolerant.
5. Control other risk factors.

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†

YES

NO

JACC 2017;70:1785 guidelines
CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER

1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)

Decision for no additional medication

Optional non-statin medications to consider

Consider ezetimibe first

NO

Consider adding or replacing with PCSK9 inhibitor second

YES

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

JACC 2017;70:1785 guidelines
Patients ≥21 Years of Age with Clinical ASCVD with Comorbidities, on Statin for Secondary Prevention

Patients with clinical ASCVD with comorbidities,* on statin for secondary prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†

YES

NO

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.‡ Consider referral to lipid specialist if statin intolerant.
5. Control other risk factors.

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†

YES

NO
CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)

Optional non-statin medications to consider

Consider either ezetimibe§ or PCSK9 inhibitor as initial non-statin agent, and addition of other agent second if needed¶

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications†

Decision for no additional medication

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
Patients ≥21 Years of Age with Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Secondary Prevention

- Patients with clinical ASCVD and baseline LDL-C ≥190 mg/dL not due to secondary causes,* on statin for secondary prevention

- Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†
  - YES
  - NO
    - 1. Address statin adherence.
    - 2. Intensify lifestyle (may consider phytosterols).
    - 3. Increase to high-intensity statin if not already taking.
    - 4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.§
      - Referral to lipid specialist recommended if statin intolerant.
    - 5. Control other risk factors.
    - 6. Consider referral to lipid specialist and RDN for all patients, especially for homozygous FH.§

- Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†
  - YES
  - NO
CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)

Optional non-statin medications to consider
Consider either ezetimibe or PCSK9 inhibitor as initial non-statin agent, and addition of other agent second if needed

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications

YES

1. Repeat clinician-patient discussion.
2. Add other non-statin medication(s) above.
3. Consider referral to lipid specialist and RDN.

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications

YES

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

NO

Referral to lipid specialist and RDN recommended
**FIGURE 3** Patients ≥21 Years of Age without Clinical ASCVD and with Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Primary Prevention

Patients without clinical ASCVD and with baseline LDL-C ≥190 mg/dL not due to secondary causes,* on statin for primary prevention

**Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally tolerated statin therapy†**

**YES**

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.‡
   - Referral to lipid specialist recommended if statin intolerant.
5. Control other risk factors.
6. Consider referral to lipid specialist and RDN for all patients.§

**NO**

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally tolerated statin therapy†

**YES**

**NO**
CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)

Optional non-statin medications to consider

Consider either ezetimibe or PCSK9 inhibitor as initial non-statin agent, and addition of other agent second if needed.

Patient has ≥50% LDL-C reduction (may consider LDL-C < 100 mg/dL or non-HDL-C < 130 mg/dL) on maximally tolerated statin/other medications†

YES
1. Repeat clinician-patient discussion.
2. Add other non-statin medication(s) above.
3. Consider referral to lipid specialist and RDN.

Patient has ≥50% LDL-C reduction (may consider LDL-C < 100 mg/dL or non-HDL-C < 130 mg/dL) on maximally tolerated statin/other medications†

NO

Referral to lipid specialist recommended

YES
Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
FIGURE 4 Patients Aged 40-75 years without Clinical ASCVD and with Diabetes and Baseline LDL-C 70-189 mg/dL, on Statin for Primary Prevention

Patients aged 40-75 years without clinical ASCVD and with diabetes and baseline LDL-C 70-189 mg/dL, on statin for primary prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or may consider non-HDL-C <130 mg/dL in patients with diabetes) on maximally tolerated statin*

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.† Consider referral to lipid specialist if statin intolerant.
4. Control other risk factors.

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or may consider non-HDL-C <130 mg/dL in patients with diabetes) on maximally tolerated statin*
CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)

Decision for no additional medication

Optional non-statin medications to consider

Consider ezetimibe‡

For the small proportion of patients in this group with 10-year ASCVD risk <7.5% and no other high-risk features, starting with moderate-intensity statin to achieve 30-49% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) is acceptable. If this level of LDL-C reduction is not achieved, consider increasing to high-intensity statin

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
FIGURE 5  Patients Aged 40-75 years without Clinical ASCVD or Diabetes, with LDL-C 70-189 mg/dL and 10-Year ASCVD Risk ≥7.5%, on Statin for Primary Prevention

Patients aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70-189 mg/dL and 10-year ASCVD risk ≥7.5%, on statin for primary prevention

- Patient has 30%-49% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on moderate intensity statin†
  - YES, and without high-risk markers*

- NO, or with high-risk markers*
  - On initial high-intensity statin
  1. Address statin adherence.
  2. Intensify lifestyle (may consider phytosterols).
  3. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.‡ Consider referral to lipid specialist if statin intolerant.
  4. Control other risk factors.

- Patient has 30-49% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on moderate intensity statin†
  - YES, and without high-risk markers*

- NO, or with high-risk markers*
Increase to high-intensity statin.

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally tolerated statin†

YES

NO, and with high-risk markers*

**CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER**
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)

Decision for no additional medication

Optional non-statin medications to consider

Consider ezetimibe§

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
EZETIMIBE

Mechanism of action: Inhibits Niemann-Pick C1 like 1 (NPC1L1) protein; reduces cholesterol absorption in small intestine

Adverse effects: Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity; combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea.

Drug–drug interactions: cyclosporine, fibrates, BAS
EZETIMIBE--MAIN TRIALS

IMPROVE-IT -- (The addition of ezetimibe to moderate-intensity statin in patients with recent **ACS** resulted in incremental lowering of LDL-C and reduced primary composite endpoint of CV death, nonfatal MI, UA requiring re-hospitalization, coronary revascularization [$30 days after randomization], or nonfatal stroke. The median follow-up was 6 years.)

SHARP -- (Simvastatin plus ezetimibe reduced LDL-C and reduced primary endpoint of first major ASCVD event [nonfatal MI or CHD death, non-hemorrhagic stroke, or any arterial revascularization procedure] **compared to placebo** over a median f/u of 4.9 years).
**PCSK9 INHIBITORS**

Mechanism of action: Human monoclonal antibody to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL.

Adverse effects: Alirocumab—nasopharyngitis, injection site reactions, influenza. Evolocumab—nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.

No evidence of increase in cognitive adverse effects observed in FOURIER or EBBINGHAUS.