Dyslipidemia Management in 2019
Role of PCSK9 inhibitors
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San Angelo Community Medical
2018 Guideline on the Management of Blood Cholesterol

GUIDELINES MADE SIMPLEx
A Selection of Tables and Figures
Goals

• Reduce Risk of Atherosclerotic Cardiovascular Disease (ASCVD) through Cholesterol Management
ASCVD
(Atherosclerotic Cardiovascular Disease)

• Coronary artery disease, peripheral artery disease, transient ischemic attack or stroke
Overview of Primary and Secondary ASCVD Prevention

This tool provides a broad overview of the 2018 Cholesterol Guideline. Please refer to the full guideline document for specific recommendations.

* Clinical ASCVD consists of acute coronary syndromes, those with history of myocardial infarction, stable or unstable angina or coronary other arterial revascularization, stroke, TIA, or peripheral artery disease including aortic aneurysm, all of atherosclerotic origin.
Primary Prevention Over The Life Span
Fourth Statin Benefit Group

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 to <190 mg/dL (≥1.8-<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, psoriasis, HIV)
- Ethnicity factors (e.g., South Asian ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/mL)

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apoB ≥1.3 mg/dL
- Ankle-brachial index (ABI) <0.9

Less than 5% “Low Risk”
Risk Discussion:
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%

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

- Family history of premature ASCVD; (males <55 years; females <65 years)
- Primary hypercholesterolemia (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).
- Metabolic syndrome (increased waist circumference, elevated TG (>175 mg/dL, elevated BP, elevated glucose, low HDL-C (<40 mg/dL in men, <50 mg/dL in women) are factors; tally of 3 makes the diagnosis)
- Chronic kidney disease (eGFR 15- 59 ml/min per 1.73 m² with or without albuminuria; not treated with dialysis or kidney transplantation)
- Chronic inflammatory conditions such as psoriasis, rheumatoid arthritis (RA) or human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)
- History of premature menopause (before age 40) and history of pregnancy-associated conditions that increase later ASCVD risk such as pre-eclampsia
- High-risk ethnicities (e.g. South Asian ancestry)
- Lipid/Biomarkers: Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dl);
  - If measured:
    - High-sensitivity C-reactive protein - (≥2.0 mg/L)
    - Elevated lipoprotein (a) - 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).
    - Elevated apo B ≥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 >160 mg/dL and constitutes a risk enhancing factor.
    - ABI <0.9
### Very High-Risk for Future ASCVD Events*

<table>
<thead>
<tr>
<th>Major ASCVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent acute coronary syndrome (within the past 12 months)</td>
</tr>
<tr>
<td>History of myocardial infarction (other than recent acute coronary syndrome event listed above)</td>
</tr>
<tr>
<td>History of ischemic stroke</td>
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<tr>
<td>Symptomatic peripheral arterial disease (history of claudication with ankle brachial index &lt;0.85, or previous revascularization or amputation)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>High-Risk Conditions</th>
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<tbody>
<tr>
<td>Age ≥65 years</td>
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<tr>
<td>Heterozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Chronic kidney disease (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 heart failure</td>
</tr>
</tbody>
</table>

*Very High Risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.
Tools

• Statins
• Ezetimibe
• PCSK9 inhibitors
### Guidelines specify statin doses

<table>
<thead>
<tr>
<th>High-intensity ↓ LDL-C by ≥50%</th>
<th>Moderate-intensity ↓ LDL-C by 30–50%</th>
<th>Low-intensity ↓ LDL-C by &lt;30%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10–20 mg</td>
<td>–</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5–10 mg</td>
<td>–</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>–</td>
<td>10 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40–80 mg</td>
<td>10–20 mg</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Fluvastatin XL</td>
<td>80 mg</td>
<td>–</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>40 mg bid</td>
<td>20–40 mg</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>2–4 mg</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

**Bold:** Statins and doses evaluated in RCTs  
**Italics:** Statins and doses approved by US FDA but not tested in RCTs reviewed  
*Should be used in patients unable to tolerate moderate-to high-intensity therapy  
Asian ancestry may modify the statin dose prescribed
Patients outside the four benefit groups: Consider statin therapy individually

Statins can be considered for patients with 10-year ASCVD risk <7.5% based on additional factors

- Elevated lifetime ASCVD risk
- LDL-C >160 mg/dL (~4.0 mmol/L)
- Other genetic hyperlipidemias
- Family history of ASCVD
- C-reactive protein >2 mg/L (~19 nmol/L)
- Ankle-brachial index <0.9
- High coronary artery calcium (CAC) score

Carotid intimal-medial thickness not recommended

Individual discussion of benefits and risks

Exceptions:
- NYHA class II–IV HF or maintenance hemodialysis – insufficient evidence


HF, heart failure
Safety Considerations

**Creatinine Kinase (CK)**
- Routine monitoring of CK not recommended
- Measurement may be useful at baseline in those at increased risk of muscle events and in patients with muscle symptoms
- Guideline provides recommendations for management of muscle symptoms

**Alanine Transaminase (ALT)**
- Baseline measurement recommended
- Routine hepatic monitoring not recommended unless symptoms suggesting hepatotoxicity are present

**Type-2 Diabetes**
- Statins modestly increase risk of type-II diabetes in patients with risk factors for diabetes
- Potential for ASCVD risk reduction benefit outweighs risk of diabetes in all but lowest risk individuals
- Evaluate for new onset diabetes according to current diabetes screening guidelines

<table>
<thead>
<tr>
<th>Statin Associated Side Effects</th>
<th>Frequency</th>
<th>Predisposing Factors</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin Associated Muscle Symptoms (SAMS)</td>
<td>Infrequent (1%–5%) in RCTs/frequent (5%–10%) in observational studies and clinical setting</td>
<td>Age, female, low BMI, high-risk medications (CYP3A4 inhibitors, OATP1B1 inhibitors), comorbidities (HIV, renal, liver, thyroid, pre-existing myopathy), Asian descent, excess alcohol, high levels of physical activity and trauma.</td>
<td>RCTs/cohorts/observational</td>
</tr>
<tr>
<td>Myalgias (CK normal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myositis/Myopathy (CK &gt;ULN) with concerning symptoms/objective weakness</td>
<td>Rare</td>
<td></td>
<td>RCTs/cohorts/observational</td>
</tr>
<tr>
<td>Rhabdomyolysis (CK &gt;10xULN + renal injury)</td>
<td>Rare</td>
<td></td>
<td>RCTs/Cohorts/observational</td>
</tr>
<tr>
<td>Statin-associated autoimmune myopathy (SAAM) (HMGCR Ab’s, incomplete resolution)</td>
<td>Rare</td>
<td></td>
<td>Case reports</td>
</tr>
<tr>
<td>New onset Diabetes Mellitus</td>
<td>Depends on population; more frequent if diabetes mellitus risk factors such as BMI ≥30, fasting blood sugar ≥100 mg/dL; metabolic syndrome or A1c ≥6% are present</td>
<td>Diabetes risk factors/metabolic syndrome</td>
<td>RCTs/Meta-analyses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-intensity statin therapy</td>
<td></td>
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</tbody>
</table>

Table 11 is continued in the next page. For references please see page 18.
<table>
<thead>
<tr>
<th>Statin Associated Side Effects</th>
<th>Frequency</th>
<th>Predisposing Factors</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Infrequent</td>
<td>RCTs/cohorts/observational</td>
<td></td>
</tr>
<tr>
<td>• Transaminase elevation 3xULN</td>
<td></td>
<td>Case reports</td>
<td></td>
</tr>
<tr>
<td>• Hepatic Failure</td>
<td>Rare</td>
<td>Case reports; no increase in memory/cognition problems in three large scale RCTs</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Memory/Cognition</td>
<td>Rare/Unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>No definite association</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Renal Function</td>
<td>Unclear/unfounded</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cataracts</td>
<td>Unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tendon Rupture</td>
<td>Unclear/unfounded</td>
<td></td>
<td></td>
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<tr>
<td>• Hemorrhagic Stroke</td>
<td>Unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Interstitial Lung Disease</td>
<td>Unclear/unfounded</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Low Testosterone</td>
<td>Unclear/unfounded</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CK indicates creatine kinase; HIV, human immunodeficiency virus; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; SAMS, statin-associated muscle symptoms; SAAM, statin-associated autoimmune myopathy; SASE, statin associated side effects; and ULN, upper limit of normal."
Review

Consensus clinical recommendations for the management of plasma lipid disorders in the Middle East


Patient populations recommended for plasma lipid screening

- Once every five years in patients ≥ 20 years old [22,24]
- T2DM [4,22]
- Arterial hypertension [4]
- Manifest ASCVD [4,22]
- Central obesity [4]
- Chronic inflammatory autoimmune disease [4]
- CKD [4,22]
- Family history of ASCVD [4]
- Offspring of patients with severe disorders of plasma lipids (e.g. FH) [4]

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; FH, familial hypercholesterolaemia; T2DM, type 2 diabetes mellitus
Statin Intolerance (SI)

- Inability to tolerate statin therapy due to muscle related side effects
- 10-25% report intolerance to statins
Statin Associated Muscle Symptoms

• Affect large muscle groups (thigh, buttocks, calves and back)

• Usually occurs in the 1st month of initiating therapy

• May occur with increase in statin dose, increase in interacting drug or increase in physical activity
Approach to Statin Intolerance

- Reduce statin dose
- Switch statin
- Decrease dose frequency (take every other day or 3 days per week)
- Checking for drug-drug interactions
  - Amiodarone (recommended max dose of simvastatin 20 mg)
Approach to Statin Intolerance

• Initiation, reduction, discontinuation, and rechallenge
AACE 2017 Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY
GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

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<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors&lt;sup&gt;a&lt;/sup&gt;/10-year risk&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Treatment goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
</tr>
</tbody>
</table>
| Extreme risk  | – Progressive ASCVD including unstable angina 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) | <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 | <70             | <100            | <80             |
| High risk     | – ≥2 risk factors and 10-year risk 10-20%  
– Diabetes or CKD 3/4 with no other risk factors | <100            | <130            | <90             |
| Moderate risk | ≤2 risk factors and 10-year risk <10%  
– Diabetes or CKD 3/4 with no other risk factors | <100            | <130            | <90             |
| Low risk      | 0 risk factors                               | <130            | <160            | NR              |

Abbreviations: ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not recommended; UKPDS = United Kingdom Prospective Diabetes Study.

<sup>a</sup>Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C.

<sup>b</sup>Framingham risk scoring is applied to determine 10-year risk.

Reproduced with permission from Garber et al. *Endocr Pract.* 2017;23:207-238.
Reduction in LDL
PCSK9 inhibitors

- Proprotein convertase subtilisin–kexin type 9 (PCSK9) promotes degradation of LDL receptors
- Diminishing the clearance of LDL from the circulation
- Mutations conveying gain or loss of function of PCSK9 result in a higher or lower level of LDL cholesterol
PCSK9 Regulates the Surface Expression of LDL-Rs by Targeting Them for Lysosomal Degradation
PCSK9 inhibitors
PCSK9 inhibitors

- Praluent (alirocumab)
- Repatha (evolocumab)
Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

ODYSSEY OUTCOMES Trial

• 18,924 pts with hx of ACS up to 1 year prior
• LDL level at least 70 mg/dL
• Statin therapy at max tolerated dose
• Alirocumab 75mg (up titrated to 150mg) to target LDL level of 25 to 50 mg/dL
ODYSSEY OUTCOMES

• Median duration of follow up 2.8 years
• Primary end-point event in 903 pts (9.5%) in alirocumab group vs 1052 (11.1%) in the placebo group
• Greater benefit noted among pts with baseline LDL >100 mg/dL
Figure 1. LDL Cholesterol Levels during the Trial
Figure 2. Cumulative Incidence of the Composite Primary End Point.
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*
FOURIER Trial

• 27,564 pts with atherosclerotic disease
• LDL of at least 70 mg/dL
• Evolocumab (140 mg q 2 wks vs 420 monthly) vs placebo
FOURIER Trial

• At 48 weeks, 59% mean reduction in LDL
• 92 mg/dL to 30 mg/dL
• Decrease in primary end point 1344 pts (9.8%) in evolocumab vs 1563 pts (11.3%) placebo
Fourier Trial

Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.
FOURIER Trial

A Primary Efficacy End Point

Hazard ratio, 0.85 (95% CI, 0.79–0.92)
P<0.001

Cumulative Incidence (%)

No. at Risk
Placebo 13,780 13,278 12,825 11,871 7610 3690 686
Evolocumab 13,784 13,351 12,939 12,070 7771 3746 689

Months
COST
• New list price for the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor is $5850 a year, down from its original list price of more than $14,000 a year
• Medicare patients, who currently pay between $280 and $370 a month in out-of-pocket costs, but will now pay $25 to $150 a month
• Three out of four Medicare patients abandon their PCSK9 inhibitor prescription mainly because of high out-of-pocket costs
Question/Comments