New Guidelines in Dyslipidemia Management

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• History of U.S. Dyslipidaemia Guideline Development
• New ACC/AHA cholesterol treatment guideline published Nov 2013
• New NICE Guidelines 2014
• Guidelines for Patients with CKD
• New ESC/EAS Guidelines 2016
• New Middle East Guidelines 2016
• 2017 Update of ESC:EAS on PCSK9 Inhibitors
# History of U.S. Dyslipidemia Guideline Development

<table>
<thead>
<tr>
<th>Year</th>
<th>ATPI</th>
<th>ATPII</th>
<th>ATPIII</th>
<th>ATPIII Update</th>
<th>ACC/AHA Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>• Exclusive focus on LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td></td>
<td>• Risk assessment guides therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td>• Lower LDL-C threshold for therapy initiation in high risk patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td>• Lower LDL-C threshold for therapy initiation in very high risk patients</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Use of moderate- or high-intensity statin therapy for patients across 4 major groups at risk for ASCVD*</td>
</tr>
</tbody>
</table>

*ASCVD, Atherosclerotic Cardiovascular Disease


NCEP ATP III Updated Report: LDL-C Goals Based on Risk Category

Increasing Risk

Lower Risk
- LDL-C Goal <160 mg/dL

Moderate Risk
- LDL-C Goal <130 mg/dL

Moderately High-Risk
- LDL-C Goal <130 mg/dL

High-Risk
- LDL-C Goal <100 mg/dL

Very High-Risk
- LDL-C Goal <100 mg/dL

Optional Goal
- LDL-C Goal <100 mg/dL
- Optional Goal <70 mg/dL

New ACC/AHA cholesterol treatment guideline published Nov 2013


What is new in the 2013 Guideline?

• Identification of 4 major statin benefit groups

• Shift away from treat to target approach

• Definitions of statin intensity provided

• New global risk assessment tool for primary prevention

• Addition of non-statin drug therapy to statins to further decrease ASCVD risk addressed

# Major Statin Benefit Groups

<table>
<thead>
<tr>
<th>ASCVD</th>
<th>LDL (mg/dL)</th>
<th>DM (40 – 75 years)</th>
<th>10 year risk ASCVD ≥ 7.5 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>&gt; 190</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>70 – 189</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>70 – 189</td>
<td>No</td>
</tr>
</tbody>
</table>

ASCVD, Atherosclerotic Cardiovascular Disease
Group 1: Patients with clinical ASCVD

Guideline Direction

“High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have clinical ASCVD, unless contraindicated.”*

*ACC/AHA Guideline 2013/p 22/secondary prevention #1
**Group 2: Patients with primary elevations of LDL–C \( \geq 190 \text{ mg/dL} \) \( \geq 4.9 \text{ mmol/L} \)**

**Guideline Direction**

“Adults \( \geq 21 \) years of age with primary LDL–C \( \geq 190 \text{ mg/dL} \) \( \geq 4.9 \text{ mmol/L} \) should be treated with statin therapy (10-year ASCVD risk estimation is not required): Use high-intensity statin therapy unless contraindicated.”*

*ACC/AHA Guideline 2013/p 22/primary prevention \( \geq 21/#2 \)
Guideline Direction

“Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated.”*

*ACC/AHA Guideline 2013/p 23/primary prevention with diabetes/# 1,2
Group 3: Patients with diabetes aged 40-75 years with LDL 70-189 mg/dL (1.8-4.9 mmol/L) and without clinical ASCVD

**Type 1 or 2 diabetes**

**Age 40–75 years**

- **Yes**
  - Estimate 10-year ASCVD risk with Pooled Cohort Equations
  - **ASCVD risk ≥7.5%**
    - **High-intensity statin***
  - **ASCVD risk <7.5%**
    - **Moderate-intensity statin†**
  - Consider statin individually

- **No**

*Expected to reduce LDL-C by ≥50%
†Expected to reduce LDL-C by 30 to <50%

Group 4: Patients without clinical ASCVD or diabetes with LDL–C 70 to 189 mg/dL (1.8 to 4.9 mmol/L) and estimated 10-year ASCVD risk ≥7.5%

Guideline Direction

“Adults 40 to 75 years of age with LDL–C 70 to 189 mg/dL (1.8 to 4.9 mmol/L), without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy.”*

*ACC/AHA Guideline 2013/p 23/Primary Prevention w/o Diabetes/#2
Guidelines use new ASCVD risk calculator

10-year risk (%) of ASCVD (non-fatal MI, CHD death, or fatal/non-fatal stroke) is calculated from simple parameters:

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>10 year risk and Lifetime Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male or female)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Race (African-American or White/other)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Treatment for high BP (yes or no)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (yes or no)</td>
<td></td>
</tr>
<tr>
<td>Smoker (yes or no)</td>
<td></td>
</tr>
</tbody>
</table>

BP, blood pressure
HDL-C, high density lipoprotein-cholesterol
SBP, Systolic blood pressure

**Guidelines specify statin doses**

<table>
<thead>
<tr>
<th></th>
<th>High-intensity ↓ <em>LDL-C</em> by ≥50%</th>
<th>Moderate-intensity ↓ <em>LDL-C</em> by 30–50%</th>
<th>Low-intensity ↓ <em>LDL-C</em> by &lt;30%*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin</strong></td>
<td>(40)–80 mg</td>
<td>10–20 mg</td>
<td>–</td>
</tr>
<tr>
<td><strong>Rosuuvastatin</strong></td>
<td>20–40 mg</td>
<td>5–10 mg</td>
<td>–</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>–</td>
<td>20–40 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td><strong>Pravastatin</strong></td>
<td>–</td>
<td>40–80 mg</td>
<td>10–20 mg</td>
</tr>
<tr>
<td><strong>Lovastatin</strong></td>
<td>–</td>
<td>40 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>Fluvastatin XL</strong></td>
<td>–</td>
<td>80 mg</td>
<td>–</td>
</tr>
<tr>
<td><strong>Fluvastatin</strong></td>
<td>–</td>
<td>40 mg bid</td>
<td>20–40 mg</td>
</tr>
<tr>
<td><strong>Pitvastatin</strong></td>
<td>–</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  

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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

Individual discussion of benefits and risks

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

HF, heart failure

A New Perspective on LDL–C and/or Non-HDL–C Treatment Goals

Lack of RCT evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets

No recommendations for or against specific LDL-C and non-HDL-C goals for primary or secondary prevention

### ASCVD Statin Benefit Groups

**Heart healthy lifestyle habits are the foundation of ASCVD prevention**

<table>
<thead>
<tr>
<th>Clinical ASCVD</th>
<th>LDL-C ≥190 mg/dL</th>
<th>Diabetes; age 40-75 years*</th>
<th>Estimated 10-yr ASCVD risk ≥7.5%; age 40-75 years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High-Intensity statin (age ≤75 years)</td>
<td>• High-intensity statin</td>
<td>• Moderate-intensity statin</td>
<td>• Moderate- to high-intensity statin</td>
</tr>
<tr>
<td>• Moderate-intensity statin if &gt;75 years or not a candidate for high-intensity statin</td>
<td>• Moderate-intensity statin if not a candidate for high-intensity statin</td>
<td>• High-intensity statin if estimated 10 year ASCVD risk ≥7.5%</td>
<td></td>
</tr>
</tbody>
</table>

**ASCVD prevention benefit of statin therapy may be less clear in other groups**. Consider additional factors influencing ASCVD risk, potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.

* With LDL-C of 70-189 mg/dL  
† Estimated using the Pooled Cohort Risk Assessment Equations

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

Lloyd-Jones DM, et al.
2016 Lipid Pathway

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
A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Endorsed by the National Lipid Association
FIGURE 1 | Patient Populations Addressed and Factors and Interventions to Consider

PATIENT POPULATIONS ADDRESSED: 4 STATIN BENEFIT GROUPS

- Adults ≥21 years of age with clinical ASCVD, on statin for secondary prevention
- Adults ≥21 years of age with LDL-C ≥190 mg/dL (not due to secondary modifiable causes), on statin for primary prevention
- Adults aged 40-75 years without ASCVD but with diabetes and LDL-C 70-189 mg/dL, on statin for primary prevention
- Adults aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of ≥7.5%, on statin for primary prevention

FACTORS TO CONSIDER
- Adherence and lifestyle
- Statin intolerance
- Control of other risk factors
- Clinician-patient discussion regarding potential benefits, potential harms, and patient preferences regarding addition of non-statin medications
- Percentage LDL-C reduction (may consider absolute LDL-C level achieved)
- Monitoring of response to therapy, adherence, and lifestyle

OPTIONAL INTERVENTIONS TO CONSIDER
- Referral to lipid specialist and registered dietitian nutritionist
- Ezetimibe
- bile acid sequestrants
- PCSK9 inhibitors
- Mipomersen, lomitapide, LDL apheresis may be considered by lipid specialist for patients with familial hypercholesterolemia

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, LDL = low-density lipoprotein, LDL-C = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin/kexin 9.
Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Issued: July 2014

NICE clinical guideline 181
guidance.nice.org.uk/cg181
Identifying and assessing cardiovascular disease (CVD) risk

* For the **primary prevention** of CVD in primary care, use a systematic strategy to identify people who are likely to be at high risk. [2008, amended 2014]

* Prioritize people for a full formal risk assessment if their estimated **10-year risk of CVD** is **10% or more**. [2008, amended 2014]

* Use the **QRISK2 risk assessment tool** to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. [new 2014]

* Do not use a risk assessment tool to assess CVD risk in people with an estimated glomerular filtration rate (**eGFR**) **less than 60 ml/min/1.73 m2** and/or **albuminuria**. These people are at increased risk of CVD. [new 2014]
**Key priorities for implementation**

*Lipid modification therapy for the primary and secondary prevention of CVD*

- Before starting lipid modification therapy for the primary prevention of CVD, **take at least 1 lipid sample** to measure a full lipid profile. This should include measurement of TC, HDL, non-HDL and triglyceride concentrations. A fasting sample is not needed. [new 2014]

- Offer **atorvastatin 20 mg** for the **primary prevention** of CVD to people who have a **10% or greater 10-year risk of developing CVD**. Estimate the level of risk using the QRISK2 assessment tool. [new 2014]

- Start statin treatment in people with CVD with **atorvastatin 80 mg**. Use a lower dose of atorvastatin if any of the following apply:
  - potential drug interactions
  - high risk of adverse effects
  - patient preference [new 2014]
Key priorities for implementation

Lipid modification therapy for the primary and secondary prevention of CVD

* Measure TC, HDL and non-HDL in all people who have been started on high-intensity statin treatment **at 3 months of treatment** and aim for **> 40% reduction in non-HDL cholesterol**. If a greater than 40% reduction in non-HDL cholesterol is not achieved:
  * discuss adherence and timing of dose
  * optimize adherence to diet and lifestyle measures

* consider increasing dose if started on less than **atorvastatin 80 mg** and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgment. [new 2014]
### Grouping of Statins as per NICE

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>–</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>–</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>–</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>–</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>38%²</td>
</tr>
</tbody>
</table>

¹ 20%–30%: low intensity.
² 31%–40%: medium intensity.
³ Above 40%: high intensity.
⁴ Advice from the MHRA: there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80 mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.
1.3 Lipid modification therapy for the primary and secondary prevention of CVD

1.3.1 Be aware that when deciding on lipid modification therapy for the prevention of CVD, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality. [2008]

1.3.2 When a decision is made to prescribe a statin use a statin of high intensity and low acquisition cost. [new 2014]
Secondary prevention

1.3.20 Start statin treatment in people with CVD with atorvastatin 80 mg. Use a lower dose of atorvastatin if any of the following apply:

- potential drug interactions
- high risk of adverse effects
- patient preference. [new 2014]

1.3.21 Do not delay statin treatment in secondary prevention to manage modifiable risk factors. [2014]

1.3.22 If a person has acute coronary syndrome, do not delay statin treatment. Take a lipid sample on admission and about 3 months after the start of treatment. [2008, amended 2014]
1.3.39 Do not stop statins because of an increase in blood glucose level or HbA$_{1c}$.
(See the recommendations on assessing for risk of diabetes mellitus in Preventing type 2 diabetes [NICE public health guidance 38].) [new 2014]
Primary prevention for people with type 1 diabetes

Recommendations in this section update and replace recommendations 1.10.1.3, 1.10.1.4, 1.10.1.5 and 1.10.2.4 from Type 1 diabetes (NICE clinical guideline 15).

1.3.23 Consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes. [new 2014]

1.3.24 Offer statin treatment for the primary prevention of CVD to adults with type 1 diabetes who:

- are older than 40 years or
- have had diabetes for more than 10 years or
- have established nephropathy or
- have other CVD risk factors. [new 2014]

1.3.25 Start treatment for adults with type 1 diabetes with atorvastatin 20 mg. [new 2014]
Primary prevention for people with type 2 diabetes

1.3.26 Offer atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014] [This recommendation updates and replaces recommendations 1.10.1.2, 1.10.1.3, and 1.10.1.5 from Type 2 diabetes (NICE clinical guideline 87).]
Guidelines for Patients with CKD

* ACC/AHA did not address specific recommendations for patients with CKD
* Appendix of Evidence Statements includes the following statement regarding use of atorvastatin for secondary prevention in patients with CKD, based on results of TNT:
  - In adults with CHD/CVD and chronic kidney disease (CKD) (excluding hemodialysis), fixed high-intensity statin treatment (atorvastatin 80 mg) that achieved a mean LDL–C of 79 mg/dL reduced CHD/CVD events more than fixed lower-dose statin treatment that achieved a mean LDL–C of 99 mg/dL (2.6 mmol/L). In this trial, the mean LDL–C levels achieved differed by 20 mg/dL (0.52 mmol/L), or 20% between the 2 groups.
* However, KDIGO (Kidney Disease Improving Global Outcomes) 2013 guidelines recommend statin therapy for CKD patients ≥50 years of age and patients 18-49 years of age with known coronary disease, diabetes, prior ischemic stroke, or 10-year CHD risk >10%
  * Once appropriate therapy has been selected, measuring LDL-C is not recommended unless results would change management
  * Escalation to reach specific LDL-C goals is no longer recommended
People with CKD

1.3.27 Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD[^].

- Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see recommendation 1.3.28) and eGFR is 30 ml/min/1.73 m^2 or more.

- Agree the use of higher doses with a renal specialist if eGFR is less than 30 ml/min/1.73 m^2. [new 2014]
## Statin Dosing Modifications in CKD

Adjust for Reduced GFR (mL/min per 1.73M²)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Atorvastatin</th>
<th>Fluvastatin</th>
<th>Lovastatin</th>
<th>Pitavastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-90 (Stage 2)</td>
<td>None</td>
<td>Max dose 40 mg/day if GFR &lt; 30</td>
<td>↓ to 50%</td>
<td>1 mg/day starting dose, not to exceed 2 mg/day</td>
<td>None</td>
<td>5 mg once daily to start, not to exceed 10 mg once daily</td>
<td>None</td>
</tr>
<tr>
<td>15-59 (Stage 3-4)</td>
<td>None</td>
<td>Max recommended dose 40 mg/day</td>
<td>↓ to 50%</td>
<td>1 mg/day starting dose, max dose 2 mg/day</td>
<td>None</td>
<td>5 mg once daily to start, not to exceed 10 mg once daily</td>
<td>↓ to 50%</td>
</tr>
<tr>
<td>&lt; 15 (Stage 5)</td>
<td>None</td>
<td>None</td>
<td>↓ to 50%</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>↓ to 50%</td>
</tr>
</tbody>
</table>

Notes: FDA restriction on 80 mg dose

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)
Use of the risk charts should be qualified by knowledge of the following aspects: factors that may modify the calculated risk (see below). Low-risk drug treatment. In particular, uncritical initiation of drug treatments of asymptomatic, age-specific risk is normally around ≤1%. Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). Moderate CKD (GFR 30–59 mL/min/1.73 m²). A calculated SCORE ≥10%.

Subjects with:
• Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima-media thickness of the carotid artery.
• DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension.
• Severe CKD (GFR <30 mL/min/1.73 m²).
• A calculated SCORE ≥10%.

**Very high-risk**

Subjects with any of the following:
• Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima-media thickness of the carotid artery.
• DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension.
• Severe CKD (GFR <30 mL/min/1.73 m²).
• A calculated SCORE ≥10%.

**High-risk**

Subjects with:
• Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg.
• Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk).
• Moderate CKD (GFR 30–59 mL/min/1.73 m²).
• A calculated SCORE ≥5% and <10%.

**Moderate risk**

SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.

**Low-risk**

SCORE <1%.

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### Recommendations for lipid control

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients at VERY HIGH CV risk, an LDL-C goal &lt;1.8 mmol/L (&lt;70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.†</td>
<td>I</td>
<td>B</td>
<td>350–353</td>
</tr>
<tr>
<td>In patients at HIGH CV risk, an LDL-C goal &lt;2.6 mmol/L (&lt;100 mg/dL), or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) is recommended.</td>
<td>I</td>
<td>B</td>
<td>350–353</td>
</tr>
<tr>
<td>In the remaining patients on LDL-C lowering treatment, an LDL-C goal &lt;3.0 mmol/L (&lt;115 mg/dL) should be considered.</td>
<td>IIa</td>
<td>C</td>
<td>350–353</td>
</tr>
</tbody>
</table>
Review

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

Nasreen Al Sayed a, *, Khalid Al Waili b, Fatheya Alawadi c, Saeed Al-Ghamdi d, Wael Al Mahmeed e, Fahad Al-Nouri f, Mona Al Rukhaimi g, Khalid Al-Rasadi h, Zuhier Awan i, Mohamed Farghaly j, Mohamed Hassanein k, Hani Sabbour l, Mohammad Zubaid m, Philip Barter n
Box 1
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
Box 4
Plasma lipid treatment goals.

**Primary treatment goal: LDL-C**

*High-risk patients*
- A 50% reduction (initial goal) AND < 1.8 mmol/L (< 70 mg/dL) (after 50% reduction achieved)

*Moderate-risk patients*
- A 30% reduction (initial goal) AND < 2.6 mmol/L (< 100 mg/dL) (after 30% reduction achieved)

**Primary treatment goal: Non-HDL-C**
- 0.8 mmol/L (30 mg/dL) higher than LDL-C target [4,71]

HDL, high-density lipoprotein; LDL-C, low-density lipoprotein; TG, triglyceride.
Table 3
Selecting a statin based on LDL-C treatment goals\textsuperscript{a} [22].

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

bid, twice daily; LDL-C, low-density lipoprotein cholesterol.
\textsuperscript{a} Individual responses to statin therapy should be expected to vary in clinical practice. Moderate- or high-intensity statin therapy is preferred unless not tolerated. Reprinted from J Clin Lipidol, Vol 9, Jacobson et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1—full report, pp. 129--169, Copyright (2015), with permission from Elsevier.
<table>
<thead>
<tr>
<th>Patient type (adults)</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 years eGFR &lt; 60 mL/min/1.73 m²</td>
<td>Statin or statin/ezetimibe</td>
</tr>
<tr>
<td>Not treated with chronic dialysis or kidney transplantation</td>
<td></td>
</tr>
<tr>
<td>(GFR categories G3a–G5)</td>
<td></td>
</tr>
<tr>
<td>≥50 years CKD and eGFR &gt; 60 mL/min/1.73 m²</td>
<td>Statin</td>
</tr>
<tr>
<td>(GFR categories G1–G2)</td>
<td></td>
</tr>
<tr>
<td>18–49 years CKD</td>
<td>Statin</td>
</tr>
<tr>
<td>Not treated with chronic dialysis or kidney transplantation</td>
<td></td>
</tr>
<tr>
<td>One or more of following present</td>
<td></td>
</tr>
<tr>
<td>• known coronary disease (myocardial infarction or coronary revascularisation)</td>
<td></td>
</tr>
<tr>
<td>• diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>• prior ischaemic stroke</td>
<td></td>
</tr>
<tr>
<td>• estimated 10-year incidence of coronary death or non-fatal myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>&gt;10%</td>
<td></td>
</tr>
<tr>
<td>Kidney transplant recipient</td>
<td>Statin</td>
</tr>
<tr>
<td>Dialysis-dependent CKD</td>
<td>Do not initiate statin (if already receiving at time of dialysis initiation, continue)</td>
</tr>
<tr>
<td>CKD and high TG</td>
<td>Lifestyle modifications</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; TG, triglyceride.
AACE 2017 Guidelines

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

EXECUTIVE SUMMARY

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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>
<tr>
<td></td>
<td></td>
<td>Non-HDL-C (mg/dL)</td>
</tr>
<tr>
<td>Extreme Risk</td>
<td>– Progressive ASCVD including unstable angina in patients after achieving an LDL-C &lt;70 mg/dL</td>
<td>&lt;55</td>
</tr>
<tr>
<td></td>
<td>– Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH</td>
<td>&lt;80</td>
</tr>
<tr>
<td></td>
<td>– History of premature ASCVD (&lt;55 male, &lt;65 female)</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Very High Risk</td>
<td>– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk &gt;20%</td>
<td>&lt;70</td>
</tr>
<tr>
<td></td>
<td>– Diabetes or CKD 3/4 with 1 or more risk factor(s)</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>– HeFH</td>
<td>&lt;80</td>
</tr>
<tr>
<td>High Risk</td>
<td>– ≥2 risk factors and 10-year risk 10%-20%</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>– Diabetes or CKD 3/4 with no other risk factors</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;90</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>≤2 risk factors and 10-year risk &lt;10%</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>– Diabetes or CKD 3/4 with no other risk factors</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;90</td>
</tr>
<tr>
<td>Low Risk</td>
<td>0 risk factors</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;160</td>
</tr>
</tbody>
</table>

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; 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.
2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia

Ulf Landmesser\textsuperscript{1*†}, M. John Chapman\textsuperscript{2†}, Jane K. Stock\textsuperscript{3}, Pierre Amarenco\textsuperscript{4}, Jill J.F. Belch\textsuperscript{5}, Jan Borén\textsuperscript{6}, Michel Farnier\textsuperscript{7}, Brian A. Ference\textsuperscript{8}, Stephan Gielen\textsuperscript{9}, Ian Graham\textsuperscript{10}, Diederick E. Grobbee\textsuperscript{11}, G. Kees Hovingh\textsuperscript{12}, Thomas F. Lüscher\textsuperscript{13}, Massimo F. Piepoli\textsuperscript{14}, Kausik K. Ray\textsuperscript{15}, Erik S. Stroes\textsuperscript{12}, Olov Wiklund\textsuperscript{16}, Stephan Windecker\textsuperscript{17}, Jose Luis Zamorano\textsuperscript{18}, Fausto Pinto\textsuperscript{19}, Lale Tokgözoglu\textsuperscript{20}, Jeroen J. Bax\textsuperscript{21}, and Alberico L. Catapano\textsuperscript{22}
Priority Patient Groups for PCSK9 Inhibition

- Patients with clinical ASCVD and substantially elevated LDL-C levels.

  Patients should be on maximally tolerated statin therapy (ideally with concomitant ezetimibe), or unable to tolerate three or more statins.

- Familial hypercholesterolaemia (FH) patients without clinical ASCVD but with substantially elevated LDL-C levels

  Patients should be on maximally tolerated statin therapy plus ezetimibe

Patients with Clinical ASCVD: When to Consider a PCSK9 Inhibitor

Patients with clinical ASCVD
(CAD, symptomatic PAD, ischaemic stroke)
On maximally tolerated statin therapy

± Ezetimibe*

* According to clinical judgement and local guidance

Two LDL-C thresholds:
>3.6 mmol/L (>140 mg/dL)

>2.6 mmol/L (>100 mg/dL) with additional indices of risk severity

- Familial hypercholesterolaemia
- Diabetes mellitus with target organ damage (e.g. proteinuria), or with a major risk factor such as marked hypertension
- Severe and/or extensive ASCVD, (refer to Box 3)
- Rapid progression of ASCVD, i.e. repeated ACS, unplanned coronary revascularizations, or ischaemic strokes within 5 years of the index event

Patients with Clinical ASCVD: When to Consider a PCSK9 Inhibitor


Two LDL-C thresholds:
- >4.5 mmol/L (>180 mg/dL)
- >3.6 mmol/L (>140 mg/dL) with additional indices of risk severity

Check for additional indices of risk severity
- Diabetes mellitus with target organ damage (e.g., proteinuria), or with a major risk factor (e.g., marked hypertension)
- Lipoprotein(a) >50 mg/dL
- Major risk factors: smoking, marked hypertension
- >40 years of age without treatment
- Premature ASCVD (<55 years in males and <60 years in females) in first-degree relatives
- Imaging indicators (refer to text)

No additional indices of risk severity
- LDL-C >4.5 mmol/L (>180 mg/dL)

Additional indices of risk severity
- LDL-C >3.6 mmol/L (>140 mg/dL)*

* Confirmed on two consecutive occasions

Consider a PCSK9 inhibitor
<table>
<thead>
<tr>
<th>Patients with clinical ASCVD</th>
<th>LDL-C threshold</th>
</tr>
</thead>
</table>
| • On maximally tolerated statin (with or without ezetimibe) or with statin intolerance  
• With additional indices of risk severity | >3.6 mmol/L (140 mg/dL)  
>2.6 mmol/L or 100 mg/dL |

**Indices of risk severity:** FH, diabetes mellitus with target organ damage or with a major risk factor such as marked hypertension; severe or extensive ASCVD; or rapid progression of ASCVD (repeated acute coronary syndrome, unplanned coronary revascularizations or ischaemic stroke within 5 years of the event).

<table>
<thead>
<tr>
<th>Familial hypercholesterolaemia patients without clinical ASCVD</th>
<th>LDL-C threshold</th>
</tr>
</thead>
</table>
| • On maximally tolerated statin plus ezetimibe  
• With additional indices of risk severity (see below) | >4.5 mmol/L (180 mg/dL)  
>3.6 mmol/L (140 mg/dL) |

**Indices of risk severity:** Diabetes mellitus with target organ damage or with a major risk factor such as marked hypertension; lipoprotein(a) >50 mg/dl; major risk factors such as smoking, marked hypertension; >40 years without treatment; premature ASCVD (<55 years in males and <60 years in females) in first degree relatives; and imaging indicators of increased risk.
Conclusions

- It has been proven in many large clinical trials that reducing level of LDL cholesterol reduces the risk of having a cardiovascular event. The benefit is proportional to the CVD risk.

- More intensive treatments are more effective in preventing clinical events

- Low LDL-C is safe

- Statins are the cornerstone of LDL-C lowering

- Addition of ezetimibe to a statin reduces ASCVD events (IMPROVE-IT trial)

- Large clinical ASCVD outcomes trials of PCSK9 inhibitors showed that these agents reduce ASCVD risk (FOURIER and SPIRE-2)
Thank you

*Questions ????*