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
## History of U.S. Dyslipidemia Guideline Development

<table>
<thead>
<tr>
<th>Year</th>
<th>Guideline</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>ATP I&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Exclusive focus on LDL-C</td>
</tr>
<tr>
<td>1993</td>
<td>ATP II&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Risk assessment guides therapy</td>
</tr>
<tr>
<td>2001</td>
<td>ATP III&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Lower LDL-C threshold for therapy initiation in high risk patients</td>
</tr>
<tr>
<td>2013</td>
<td>ATP III Update&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Lower LDL-C threshold for therapy initiation in very high risk patients</td>
</tr>
<tr>
<td>2013</td>
<td>ACC/AHA Guidelines&lt;sup&gt;5&lt;/sup&gt;</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

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NCEP ATP III Updated Report: Risk Categories

Increasing Risk

Lower Risk
- 0-1 risk factor

Moderate Risk
- 2+ risk factors
- 10-year risk <10%

Moderately High-Risk
- 2+ risk factors
- 10-year risk 10-20%

High-Risk
- CHD
- CHD risk equivalents
- 10-year risk >20%

Very High-Risk
- Established CVD plus:
  - Multiple major risk factors
  - Severe and poorly controlled risk factors
  - Multiple risk factors of metabolic syndrome
  - ACS

ACS=acute coronary syndromes; CHD=coronary heart disease; CVD=cardiovascular disease.

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

New ACC/AHA cholesterol treatment guideline published Nov 2013


AHA, American Heart Association
ACC, American College of Cardiology
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
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 ≥190 mg/dL (≥4.9 mmol/L)

Guideline Direction

“Adults ≥21 years of age with primary LDL–C ≥190 mg/dL (≥4.9 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 ≥21/#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

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

No

Consider statin individually

Yes

Estimate 10-year ASCVD risk with Pooled Cohort Equations

ASCVD risk ≥7.5%

High-intensity statin*

ASCVD risk <7.5%

Moderate-intensity statin†

*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
The potential for an ASCVD risk reduction benefit clearly exceeds the potential for adverse effects in adults within the 4 major statin groups.

<table>
<thead>
<tr>
<th>ASCVD</th>
<th>LDL (mg/dL)</th>
<th>DM (40 – 75 yrs)</th>
<th>10 year risk ASCVD ≥ 7.5 %</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>&lt; 75 yrs High Intensity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; 75 yrs Moderate Intensity</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>&gt; 190</td>
<td>-</td>
<td>High Intensity</td>
</tr>
<tr>
<td>3a</td>
<td>No</td>
<td>70 – 189</td>
<td>Yes</td>
<td>Moderate Intensity</td>
</tr>
<tr>
<td>3b</td>
<td>No</td>
<td>70 – 189</td>
<td>Yes</td>
<td>High Intensity</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>70 – 189</td>
<td>No</td>
<td>Moderate to High Intensity</td>
</tr>
<tr>
<td>No</td>
<td>70 – 189</td>
<td>No</td>
<td>5 - 7.5 %</td>
<td>Moderate Intensity</td>
</tr>
<tr>
<td>No</td>
<td>70 – 189</td>
<td>No</td>
<td>&lt; 5 %</td>
<td></td>
</tr>
</tbody>
</table>
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>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male or female)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Race (African-American or White/other)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
</tr>
<tr>
<td>Treatment for high BP (yes or no)</td>
</tr>
<tr>
<td>Diabetes (yes or no)</td>
</tr>
<tr>
<td>Smoker (yes or no)</td>
</tr>
</tbody>
</table>

10 year risk and Lifetime Risk
**Guidelines specify statin doses**

<table>
<thead>
<tr>
<th></th>
<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>(40)–80 mg</td>
<td>10–20 mg</td>
<td>–</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>20–40 mg</td>
<td>5–10 mg</td>
<td>–</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>–</td>
<td>20–40 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>–</td>
<td>40–80 mg</td>
<td>10–20 mg</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>–</td>
<td>40 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Fluvastatin XL</td>
<td>–</td>
<td>80 mg</td>
<td>–</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>–</td>
<td>40 mg bid</td>
<td>20–40 mg</td>
</tr>
<tr>
<td>Pitavastatin</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

## Summary: 2013 Guideline Recommendations for Statin Therapy

### 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

Recommendations for Non-statin Therapies

* No data supporting the routine use of non-statin drugs combined with statin therapy to further decrease ASCVD events

* In high-risk patients who have an insufficient response to statin therapy, or who are unable to tolerate either a statin or the recommended statin intensity, addition of a non-statin cholesterol-lowering therapy can be considered

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
Since the publication of the 2013 ACC/AHA cholesterol guidelines, RCTs evaluating the safety and efficacy of non-statin therapies have provided important information regarding the potential benefits and harms of these agents in ASCVD risk reduction when used in combination with evidence-based statin therapy.

In addition, the approval of 2 PCSK9 inhibitors for LDL-C lowering in specific high-risk patients has resulted in gaps in expert guidance regarding the role of available non-statin therapies.
This Expert Consensus Decision Pathway addresses current gaps in care for LDL-C lowering to reduce ASCVD risk and recommendations build on the evidence base established by the 2013 ACC/AHA cholesterol guideline.

Recommendations attempt to provide practical guidance for clinicians and patients regarding the use of non-statin therapies to further reduce ASCVD risk in situations not covered by the guideline until such time as the scientific evidence base expands and cardiovascular outcomes trials are completed with new agents for ASCVD risk reduction.
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
- Niacin
- 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.
FIGURE 2B  Patients 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 may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†

YES

NO

1. Address statin adherence.
2. Intensity 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.‡
5. Consider referral to lipid specialist if statin intolerant.
6. Control other risk factors.

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

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 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 4)

Decision for no additional medication

Optional non-statin medications to consider

Consider ezetimibe first.§

YES

NO

Consider adding or replacing with PCSK9 inhibitor second.¶

YES

NO

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

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
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
Key priorities for implementation – NICE 2014

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

#### Reduction in LDL-C

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>–</td>
<td>–</td>
<td>21%(^1)</td>
<td>27%(^1)</td>
<td>33%(^2)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>–</td>
<td>20%(^1)</td>
<td>24%(^1)</td>
<td>29%(^1)</td>
<td>–</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>–</td>
<td>27%(^1)</td>
<td>32%(^2)</td>
<td>37%(^2)</td>
<td>42%(^3,4)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>–</td>
<td>37%(^2)</td>
<td>43%(^3)</td>
<td>49%(^3)</td>
<td>55%(^3)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>38%(^2)</td>
<td>43%(^3)</td>
<td>48%(^3)</td>
<td>53%(^3)</td>
<td>–</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]
NICE 2014 - Do not delay in secondary prevention

Secondary prevention

1.3.20 Start statin treatment in people with CVD with atorvastatin 80 mg\textsuperscript{[i]}. 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$_1$c. (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).]
1.3.45 Do not routinely offer fibrates for the prevention of CVD to any of the following:

- people who are being treated for primary prevention
- people who are being treated for secondary prevention
- people with CKD
- people with type 1 diabetes

people with type 2 diabetes. [new 2014]

**Combination therapy for preventing CVD**

1.3.50 Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD. [new 2014]
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\[1\].

- 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

<table>
<thead>
<tr>
<th></th>
<th>60-90 (Stage 2)</th>
<th>15-59 (Stage 3-4)</th>
<th>&lt; 15 (Stage 5)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>None</td>
<td>Max dose 40 mg/day if GFR &lt; 30</td>
<td>Max recommended dose 40 mg/day</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>None</td>
<td>↓ to 50%</td>
<td>↓ to 50%</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>None</td>
<td>1 mg/day starting dose, not to exceed 2 mg/day</td>
<td>1 mg/day starting dose, max dose 2 mg/day</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>None</td>
<td>5 mg once daily to start, not to exceed 10 mg once daily</td>
<td>5 mg once daily to start, not to exceed 10 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>None</td>
<td>↓ to 50%</td>
<td>↓ to 50%</td>
<td>FDA restriction on 80 mg dose</td>
</tr>
</tbody>
</table>

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)
Table 5  Risk categories

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Description</th>
</tr>
</thead>
</table>
| 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%.                                                                  |

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Recommendations for lipid control

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class^a</th>
<th>Level^b</th>
<th>Ref^c</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>
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 6
Recommendations for managing plasma lipids in patients with chronic kidney disease [23].

<table>
<thead>
<tr>
<th>Patient type (adults)</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 years</td>
<td>Statin or statin/ezetimibe</td>
</tr>
<tr>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>Not treated with chronic dialysis or kidney transplantation (GFR categories G3a–G5)</td>
<td></td>
</tr>
<tr>
<td>≥50 years</td>
<td>Statin</td>
</tr>
<tr>
<td>CKD and eGFR &gt; 60 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>(GFR categories G1–G2)</td>
<td></td>
</tr>
<tr>
<td>18–49 years</td>
<td>Statin</td>
</tr>
<tr>
<td>CKD</td>
<td></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 ENDOCRINOLISTS 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$^a$/10-year risk$^b$</th>
<th>Treatment goals</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
<td>Non-HDL-C (mg/dL)</td>
<td>Apo B (mg/dL)</td>
<td></td>
</tr>
</tbody>
</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) | <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% | <100           | <130 | <90 |
| Low Risk       | 0 risk factors                     | <130           | <160 | NR |

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.

$^a$ 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.

$^b$ Framingham risk scoring is applied to determine 10-year 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 are ongoing. However, there are some preliminary, post-hoc shorter-term CV data available suggesting that these agents may reduce ASCVD risk.
Thank you

*Questions ????