

Dyslipidemia ATP4

The American college of cardiology (ACC) and American Heart Association (AHA) in combination with National Heart, Lung and blood institute (NHLBI) have released 4 new guidelines. At the invitation of the National Heart, Lung, and Blood Institute (NHLBI), The American Heart Association (AHA) and the American College of Cardiology (ACC) are officially assuming the joint governance, management and public distribution of five clinical practice guidelines focused on cardiovascular prevention, according to an editorial statement published in both the Journal of the American College of Cardiology and Circulation. The guidelines will provide recommendations on hyperlipidemia, hypertension, cardiovascular risk assessment, cardiovascular lifestyle interventions and obesity.

Dyslipidemia: A disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, the "bad" low density lipoprotein (LDL) cholesterol and the triglyceride concentrations, and a decrease in the "good" high-density lipoprotein (HDL) cholesterol concentration in the blood.

First step: determine the goal for dyslipidemia treatment (primary prevention vs. secondary prevention)

Primary prevention for:

- 1- LDL-C \geq 190 mg/dl
- 2- Diabetes and aged 40-75 years with LDL-C between 70-189 mg/dl
- 3- No diabetes and estimated 10 year ASCVD risk of \geq 7.5 % who are between 40 to 75 years of age with LDL-C between 70-189 mg/dl

Secondary prevention for:

- 1- Patients with known coronary heart disease (CHD; including myocardial infarction, angina, and prior coronary revascularization)
- 2- other cardiovascular disease (CVD; including stroke, transient ischemic attack, and peripheral arterial disease)
- 3- combinations of risk factors that result in a 10-year risk of ASCVD events of more than 20 percent
- 4- Chronic kidney disease with estimated GFR $<$ 45ml/min/1.73m²
- 5- Risk equivalent for CV in diabetic patients:
Although some guidelines have considered all patients with diabetes mellitus (DM) to have a risk of CV events similar to patients with known CVD, this actually averages events across patients with widely differing risks of CHD. Issues that may affect risk with DM include patient age, sex, other CV risk factors, duration of DM, and whether the patient has type 1 or type 2 DM. Given this, it is preferable to calculate patient-specific risks rather than to simply consider all patients with DM to require treatment for secondary prevention, particularly in patients

who are under age 60 without multiple cardiovascular risk factors. A downloadable calculator for this purpose is available for patients with type 2 DM from the UK Prospective Diabetes Study (www.dtu.ox.ac.uk/riskengine)

If a patient-specific risk calculator cannot be accessed, we suggest considering the following patients with diabetes mellitus (DM) to have a similar risk those with known CV disease:

1. Men over age 40 with type 2 DM and any other CHD risk factor, or over age 50 with or without other CHD risk factors
2. Women over age 45 with type 2 DM and any other CHD risk factor, or over age 55 with or without other CHD risk factors
3. Men or women of any age who have had DM (type 1 or type 2) for more than 20 years if they have another risk factor or more than 25 years without another risk factor

Second step: Lifestyle modification for primary and secondary prevention

1- Weight loss FOR overweight patients

- A- Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats.
- B- Aim for a dietary pattern that achieves 5-6% of calories from saturated fat.
- C- Reduce percent of calories from saturated fat.
- D- Reduce percent of calories from trans-fat.
- E- Diet recommendations for blood pressure lowering (Lower sodium intake, Consume no more than 2400 mg of sodium per day)

2- Aerobic exercise

1. Aerobic exercise

Frequency: 3-5 days/week

Intensity: 50-80% of exercise capacity

Duration: 20-60 minutes

Modalities: Examples include walking, treadmill, cycling, rowing and stair climbing

3- Smoking cessation

Intensities of Statin Therapy:

High-Intensity Statin

Daily dose lowers LDL-C, on average by approximately $\geq 50\%$:

Atorvastatin 40-80 mg

Rosuvastatin 20-(40) mg

Moderate-Intensity Statin

Daily dose lowers LDL-C, on average by approximately 30% to $< 50\%$:

Atorvastatin 10-(20) mg

Fluvastatin 40 mg bid

Fluvastatin XL 80 mg

Lovastatin 40 mg

Pitavastatin 2-4 mg

Pravastatin 40-(80) mg

Rosuvastatin (5)-10 mg

Simvastatin 20-40 mg

Low-Intensity Statin

Daily dose lowers LDL-C, on average by approximately $< 30\%$:

Fluvastatin 20-40 mg

Lovastatin 20 mg

Simvastatin 10 mg

Pitavastatin 1 mg

Pravastatin 10-20 mg

Third step: pharmacological treatment for primary prevention:

- When a pharmacologic agent is required for treatment in primary prevention, a statin is the preferred medication. If a statin is not tolerated or a particular LDL-C goal is not achieved on a statin alone, we suggest not administering or adding a nonstatin lipid-lowering medication.
- 1- Cardiovascular risk should be calculated by Pooled Cohort Equations CV risk calculator (ACC/AHA Calculator) which can be found on (http://tools.cardiosource.org/ASCVD-Risk-Estimator/#page_recommendation) to determine 10 year risk factor for CV events.
 - 10 year ASCVD risk:** a quantitative estimation of absolute risk based upon data from representative population samples. Example: if 10 year ASCVD risk estimates is 10%, this indicates that among 100 patients with the entered risk factor profile, 10 would be expected to have a heart attack or stroke in the next 10 years.

The calculator includes the following parameters:

1. Gender (male/female)
2. Age
3. Race (white/African American /other)
4. HDL-cholesterol (mg/dl)
5. Total cholesterol (mg/dl)
6. Diabetes (yes/no)
7. Treatment of hypertension
8. Systolic blood pressure
9. Smoker (yes/no)

2. The American College of Cardiology/American Heart Association (ACC/AHA) makes the following recommendations for:

-Adults ≥ 21 years of age with primary LDL-C ≥ 190 mg/dL should be treated with high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. (I B)

THEN

If these individuals with an untreated primary LDL-C ≥ 190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. (IIa B)

THEN

If still untreated primary LDL-C ≥ 190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL-C. (IIb C)

Following recommendations for:

1. adults ages 40 to 75
2. without known CVD
3. LDL-C between 70 mg/dL (1.81 mmol/L) and 189 mg/dL (4.90 mmol/L) :

-In those **without** diabetes:

-Treat those with an estimated 10-year CVD risk ≥ 7.5 percent with moderate- to high-intensity Statin therapy (1A)

-It is reasonable to offer treatment with moderate intensity statin therapy to those with an estimated 10-year CVD risk between 5.0 and 7.5 percent (11a B)

-In those **with** diabetes:

-Treat with at least moderate statin therapy (1A)

-High-intensity statin therapy is reasonable in those with an estimated 10-year CVD risk ≥ 7.5

-In adults with diabetes mellitus, who are < 40 or > 75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to

consider patient preferences when deciding to initiate, continue, or intensify statin therapy.
(IIa C)

-Additionally, for adults with an LDL-C ≥ 190 mg/dL [4.92 mmol/L] the ACC/AHA recommends treatment with high-intensity statin therapy and consideration of use of nonstatin drugs to further reduce the LDL-C.

Third step: pharmacological treatment for secondary prevention:

The following management:

- 1- Age ≤ 75 y and no safety concerns: High-intensity statin
- 2- Age >75 y or safety concerns: Moderate-intensity statin

- In patients with known CVD or at similar risk who can tolerate statin therapy, we suggest treatment with an intensive dose of a statin (e.g., atorvastatin 40 to 80 mg; rosuvastatin 20 to 40 mg) independent of the baseline LDL-C. Intensive statin therapy with atorvastatin 80 mg daily reduces mortality in patients with an acute coronary syndrome and is recommended as initial therap.

In usual risk patients with stable CVD:

- 1- If patients do not achieve at least a 50 percent reduction in LDL-C to an LDL-C below 100 mg/dL (2.6 mmol/L), we maximize statin therapy if tolerated.
- 2- If patients remain above the goals on maximal statin therapy, in most patients we add a second LDL lowering agent.
- 3- In patients who started with an LDL-C near goal and achieve an LDL-C below 70 mg/dL (1.8 mmol/L) but not a 50 percent reduction in LDL-C on maximal statin therapy, we would not add a second agent.

In patients at very high risk for CVD events such as those in the proposed **NCEP guidelines** (Established coronary heart disease **PLUS** Multiple major risk factors (especially diabetes) **OR** Severe and poorly controlled risk factors (especially continued smoking) **OR** Multiple risk factors of the metabolic syndrome (especially triglycerides ≥ 200 plus non-HDL-C ≥ 130 plus HDL-C < 40) **OR** Acute coronary syndrome) :

- 1- If patients do not achieve at least a 50 percent reduction in LDL-C to an LDL-C below 70 mg/dL (1.8 mmol/L), we maximize statin therapy if tolerated.
- 2- If patients remain above these goals on maximal statin therapy, we add a second LDL lowering agent.

The goal of LDL-C:

LDL-C less than 100 mg/dL (2.6 mmol/L). Even more aggressive target LDL-C goals of 70 to 80 mg/dL (1.8 to 2.1 mmol/L) may be appropriate in some patients.

NON-STATIN therapy:

Fibrates — the major effects of the fibrates are to lower plasma triglyceride and raise HDL-C levels. They are effective for the treatment of hypertriglyceridemia and combined hyperlipidemia with or without hypoalphalipoproteinemia. There is an increased risk of muscle toxicity in patients taking some fibrates and a statin.

Nicotinic acid — Nicotinic acid (niacin) is effective in improving lipid parameters in patients who have hypercholesterolemia or combined hyperlipidemia associated with normal and low levels of HDL-C (hypoalphalipoproteinemia). The HD raising properties of nicotinic acid occur with dosages as low as 1 to 1.5 g/day. In contrast, while modest VLDL-C and LDL-C lowering effects can occur at doses of 1.5 to 2.0 g/day, doses above this amount (3 g/day) often produce greater effects. The use of nicotinic acid is often limited by poor tolerability, and there are concerns about the safety of nicotinic acid as well as its efficacy for clinical endpoints.

Ezetimibe — modestly lowers the LDL-C when used alone and may be helpful for avoiding high doses of statins (and potentially increased susceptibility to muscle injury) in patients who do not meet cholesterol goals on statin therapy alone. However, the clinical benefits of either ezetimibe monotherapy or combining ezetimibe with statin therapy remain to be proven.

Bile acid sequestrants — Bile acid sequestrants are effective in patients with mild to moderate elevations of LDL-C. Low doses (8 g/day of cholestyramine or 10 g/day of colestipol) can reduce LDL-C by 10 to 15 percent. A more pronounced reduction can be achieved at maximal recommended doses (24 and 30 g/day, respectively). A similar reduction in LDL cholesterol can be achieved with 1.5 to 4.5 g/day of colesevelam. Bile acid sequestrants are also effective when used in combination with a statin or nicotinic acid in patients with markedly elevated plasma levels of LDL-C. The use of a bile acid sequestrant is often limited by side effects.

Statin Safety Recommendations

Characteristics predisposing individuals to statin adverse effects include, but are not limited to:

1. Multiple or serious comorbidities, including impaired renal or hepatic function.
2. History of previous statin intolerance or muscle disorders.
It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: (IIa B)
 1. If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK, creatinine, and a urinalysis for myoglobinuria.
 2. If mild to moderate muscle symptoms develop during statin therapy:

- A- Discontinue the statin until the symptoms can be evaluated.
- B- Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases).
- C- If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy.
- D- Once a low dose of a statin is tolerated, gradually increase the dose as tolerated.
- E- If, after 2 months without statin treatment, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms listed above.
- F- If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose.

3. Unexplained ALT elevations >3 times ULN.

- 1. Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiating statin therapy. (I B)
- 2. During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). (IIa C)

4. Patient characteristics or concomitant use of drugs affecting statin metabolism.

5. >75 years of age

- For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug. (IIa C)

Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)

Age ≥ 21 y and a candidate for statin therapy

Definitions of High- and Moderate-Intensity Statin Therapy*

Moderate Daily dose lowers LDL-C by approx. 30% to <50%	High Daily dose lowers LDL-C by approx. $\geq 50\%$
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Clinical ASCVD

Yes

Age ≤ 75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

Yes

Age >75 y **OR** if not candidate for high-intensity statin
Moderate-intensity statin

No

LDL-C ≥ 190 mg/dL

Yes

High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

No

Diabetes
Type 1 or 2
Age 40-75 y

Yes

Moderate-intensity statin

Yes

Estimated 10-y ASCVD risk $\geq 7.5\%$ [†]
High-intensity statin

No

DM age <40 or >75 y

Primary prevention
(No diabetes, LDL-C 70-189 mg/dL, and not receiving statin therapy)
Estimate 10-y ASCVD risk every 4-6 years
Pooled Cohort Equations[†]

<5% 10-y ASCVD risk[‡]

Age <40 or >75 y and LDL-C <190 mg/dL[‡]

$\geq 7.5\%$ 10-y ASCVD risk
(Moderate- or high-intensity statin)

5% to $<7.5\%$ 10-y ASCVD risk
(Moderate-intensity statin)

In selected individuals, additional factors may be considered to inform treatment decision making[§]

Clinician-Patient Discussion
Prior to initiating statin therapy, it is important to discuss:

1. Potential for ASCVD risk-reduction benefits^{||}
2. Potential for adverse effects and drug-drug interactions^{*||}
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C ≥ 160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal CAC score or ABI, or hs-CRP ≥ 2 mg/L[§]

No to statin

Yes to statin

Emphasize adherence to lifestyle
Manage other risk factors
Monitor adherence

Encourage adherence to lifestyle
Initiate statin at appropriate intensity
Manage other risk factors
Monitor adherence^{*}

Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments

References:

1. Up-to-date

Robert S Rosenson. Jul 25, 2014. Treatment of lipids (including hypercholesterolemia)

<http://www.uptodate.com.lib.just.edu.iq/contents/definition-and-screening-for-dyslipidemia-in-children?source=preview&search=%2Fcontents%2Fsearch&anchor=H896751#H896751>

2. http://tools.cardiosource.org/ASCVD-Risk-Estimator/#page_statin_dose

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