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EDITORIAL

New (2018) American (ACC/AHA) Cholesterol Guidelines: Main Messages

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Abstract

Key points and main messages of the new (2018) American Guidelines on cholesterol management are herein provided with tabulation of the risk assessment tools, the classification of statins according to their therapeutic intensity and desired lipid levels in children. *Rhythmoss 2019;14(1):1-4.*

Key Words: cholesterol; cholesterol guidelines; cardiovascular disease; atherosclerosis; coronary artery calcium; statins; PCSK9 inhibitors; diet; primary prevention; secondary prevention; diabetes mellitus

Abbreviations: CAC = coronary artery calcium; CV = cardiovascular; CVD = cardiovascular disease; LDL = low-density lipoprotein

The new (2018) American guidelines on cholesterol management provide a more personalized approach in risk assessment (**Tables 1 & 2**) and the

decision to start therapy, with new options for those of very high-risk for atherosclerotic cardiovascular (CV) disease (CVD), while they have returned to the use of low-density lipoprotein (LDL)-cholesterol level targets.¹ These guidelines also put emphasis on lifestyle modification and shared decision-making. They discuss the value of using coronary artery calcium (CAC) scores for some patients (some consider this excessively costly), the importance of considering family history for risk calculation, the effect of age (<40 and >75) on the CV risk (considering it appropriate to treat older people). The level of LDL cholesterol >160 mg/dl is considered “very high”; a level of <100 mg/dl is considered to be associated with lower CV risk, but for high risk patients the level that should be attained is <70 mg/dl. The guidelines also cover the pediatric population. Children of very high-risk families can be tested as early as at the age of 2. However, for the majority of children, the recommendation is to have an initial test between ages 9 and 11, and then a follow-up test between the ages of 17 and 21.

An aggressive approach is recommended for individuals who have atherosclerotic CVD, a very high cholesterol level, or diabetes mellitus (DM). In these groups, in addition to a healthy lifestyle, a statin is recommended, if tolerated, and, when needed, additional

medications, depending on the LDL-cholesterol level. The guidelines encourage increased collaboration between physicians and their patients (participatory medicine / shared decision-making) that will include discussion of *risk-enhancing factors* (Table 2).

Table 1. Variables in risk assessment tools

- Age • Sex • Race • Total cholesterol • HDL-cholesterol
- Systolic BP • Antihypertensive therapy • History of diabetes mellitus • Current smoking • hsCRP level
- Parental history of MI before age 60

BP = blood pressure; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; MI = myocardial infarction

For *primary prevention*, atherosclerotic CVD risk factors should be sought. One major CVD risk factor is elevated measured serum LDL-cholesterol. Screening can be performed with fasting or nonfasting measurement of lipids. In children, adolescents (10-19 years of age), and young adults (20-39 years of age), priority should be given to estimation of lifetime risk and promotion of healthy lifestyle. Drug therapy is needed only in selected patients with moderately high (≥ 160 mg/dL) or very high LDL-cholesterol levels (> 190 mg/dL). Three major higher-risk categories are patients with severe hypercholesterolemia (LDL-cholesterol levels ≥ 190 mg/dL), adults with DM, and adults 40 - 75 years of age, who are candidates for immediate statin therapy without further risk assessment.

Table 2. Risk-enhancing factors

- Family history of premature atherosclerotic CVD (men: < 55 y, women: < 65 y)
- Primary hypercholesterolemia (LDL-cholesterol, 160–189 mg/dL; non-HDL-cholesterol 190–219 mg/dL)
- Metabolic syndrome
- Chronic kidney disease (eGFR < 60 mL/min/1.73 m²)
- Chronic inflammatory disease (e.g. psoriasis, rheumatoid arthritis, or HIV/AIDS)
- History of premature menopause (< 40 y) or pregnancy-associated conditions that increase later CVD risk such as preeclampsia
- High-risk race/ethnicities (e.g., South Asian ancestry)
- Lipid/biomarkers
 - Persistently \uparrow triglycerides (≥ 175 mg/dL); o if measured:
 - \uparrow hsCRP (≥ 2.0 mg/L)
 - \uparrow Lp(a): ≥ 50 mg/dL or ≥ 125 nmol/L
 - \uparrow apoB ≥ 130 mg/dL:
 - ABI < 0.9

ABI = ankle-brachial index AIDS = acquired immunodeficiency syndrome; ABI, apoB = apolipoprotein B; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; hsCRP = high-sensitivity C-reactive protein; Lp(a)= lipoprotein (a)

Main Messages

Some of the main messages are herein outlined:

1. A **heart-healthy lifestyle** with healthy diet and regular physical activity is emphasized for all ages.
2. Use of *high-intensity statin* therapy (Table 3) at maximal tolerated doses is recommended in patients with **clinical atherosclerotic CVD** to lower LDL cholesterol by $\geq 50\%$.
3. **Cholesterol targets** return: for very high-risk CVD patients (history of multiple major CVD events or 1 major CVD event and multiple high-risk conditions), the target for LDL-cholesterol should be < 70 mg/dL.
4. **A stepped approach is recommended: when the desired target is not achieved with a statin, addition of non-statins to statin therapy may be considered.**
 - 4a. Non-statins to add comprise oral *ezetimibe* (prevents the absorption of cholesterol in the intestine) or injectable *PCSK9 inhibitor*²
 5. In patients at very high risk whose LDL-cholesterol level remains ≥ 70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (> 3 years) is uncertain and cost-effectiveness is currently low
 6. **In patients with LDL-cholesterol ≥ 190 mg/dL, high-intensity statin therapy should be started without bothering to calculate 10-year CVD risk.** However, in this group, the target is < 100 mg/dL instead of < 70 mg/dL, probably because there is no evidence, yet, of actual atherosclerosis.
 - 6a. If the LDL-cholesterol remains ≥ 100 mg/dL, adding ezetimibe is reasonable.
 - 6b. If the LDL-cholesterol remains ≥ 100 mg/dL despite statin plus ezetimibe therapy and the patient has multiple factors that increase subsequent risk of CVD events, a PCSK9 inhibitor may be considered, with the caveats of uncertain long-term safety (> 3 years) and high cost of this therapy.
 7. **In patients 40 - 75 years of age with DM and LDL-cholesterol ≥ 70 mg/dL**, moderate-intensity statin therapy should be used; **high-intensity statin therapy should be used in those at higher risk** (multiple risk factors or age 50-75 years)

In the group of healthy people with moderately elevated cholesterol levels, the decision to start a statin will depend on the presence of other CV risk factors, such as smoking, hypertension, DM, family history of premature atherosclerotic CVD, and the LDL-cholesterol

level; other factors might comprise ethnicity (e.g. South Asian ethnicity) or premature menopause (before age 40), metabolic syndrome, elevated triglycerides or elevated high-sensitivity C-reactive protein levels (a marker of inflammation), might also direct towards starting someone on a statin. Finally, the guidelines have included coronary artery calcium (CAC) as determined by (simplified) CT scan as a tool to decide about the initiation of statin therapy in certain cases.³ Patient preferences and cost (though most statins are now generic) need also be considered. Online risk calculators may be helpful.

8. In adults 40-75 years of age evaluated for primary CVD prevention, a physician–patient risk discussion should precede initiation of statin therapy. Risk discussion should include a review of major risk factors (e.g., cigarette smoking, high blood pressure, LDL-cholesterol, hemoglobin A1C (if relevant), and calculated 10-year CV risk); the presence of risk-enhancing factors (**Table 2**); the potential benefits of lifestyle and statin therapies; the potential for adverse effects and drug–drug interactions; consideration of costs of statin therapy; and patient preferences and values in shared decision-making.

9. In adults 40-75 years of age without DM and with LDL-cholesterol levels ≥ 70 mg/dL, at a 10-year CV risk of $\geq 7.5\%$, one should start a moderate-intensity statin depending on the outcome of the discussion about treatment options. Risk-enhancing factors favor statin therapy (**Table 2**). If risk status is uncertain, consider using CAC to improve specificity. If statins are indicated, LDL-cholesterol levels should be reduced by $\geq 30\%$, and if 10-year risk is $\geq 20\%$, LDL-cholesterol levels should be reduced by $\geq 50\%$.

10. In adults 40-75 years of age without DM and 10-year risk of 7.5-19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (Table 2). Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk).

11. In adults 40-75 years of age without DM and with LDL-cholesterol levels ≥ 70 mg/dL to 189 mg/dL, at a 10-year CVD risk of $\geq 7.5\%$ to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC. If CAC is zero, treatment with statin therapy may be withheld or postponed, except in cigarette smokers, those with DM, and those with a strong family history of premature CVD. A CAC score of 1-99 favors statin therapy, especially in those ≥ 55 years of age. For any patient, if the CAC score is ≥ 100 Agatston units or ≥ 75 th percentile, statin therapy is indicated unless otherwise decided during the clinician–patient risk discussion.

12. Adherence and percentage response to LDL-cholesterol–lowering agents and lifestyle changes should be assessed with repeat lipid measurement 4-12 weeks after statin initiation or dose adjustment, repeated every 3-12 months as needed. Responses to lifestyle and statin therapy should be defined by percentage reductions in LDL-cholesterol levels compared with baseline. In CVD patients at very high-risk, triggers for adding non-statin drug therapy are defined by threshold LDL-cholesterol levels ≥ 70 mg/dL on maximal statin therapy.

Table 3. Intensity of statin therapy

- **High-intensity statins ($\geq 50\%$ LDL-cholesterol lowering)**
Atorvastatin 40-80 mg / Rosuvastatin 20-40 mg
- **Moderate intensity statins (30-50% LDL-cholesterol lowering)**
Atorvastatin 10-20 mg / Rosuvastatin 5-10 mg / Simvastatin 20-40 mg / Pravastatin 40-80 mg / Lovastatin 40-80 mg / Fluvastatin XL 80 mg / Fluvastatin 40 mg bid / Pitavastatin 1-4 mg
- **Low-intensity statins ($< 30\%$ LDL-cholesterol lowering)**
Simvastatin 10 mg / Pravastatin 10-20 mg / Lovastatin 20 mg / Fluvastatin 20-40 mg

Risk-Enhancing Factors

A companion report was published simultaneously with the cholesterol guidelines and provides guidance about the use of quantitative risk assessment in primary prevention for CVD.⁴ The risk calculator that uses several variables (**Table 1**) was introduced in the 2013 guidelines and remains an important tool to help health care providers identify a patient’s 10-year risk for CVD.⁵ An additional tool to this calculator is provided by the current guidelines, a list of “*risk-enhancing factors*” (**Table 2**) urging physicians to talk with patients about these factors that can provide a more personalized approach to a person’s risk, in addition to traditional risk factors such as smoking, high blood pressure and high blood glucose to address under- or over-estimated risk in some individuals. This additional information will be helpful in determining what kind of treatment plan a person needs. Risk-enhancing factors include a positive family history of premature CVD; specific racial/ethnic backgrounds; and certain comorbidities such as metabolic syndrome, chronic kidney disease, chronic inflammatory conditions, premature menopause or pre-eclampsia, and certain lipid and other biomarkers (**Table 2**).

Primary and Secondary Prevention

In primary and secondary prevention, when high cholesterol cannot be controlled by diet or exercise, the first line of treatment is typically statins, mostly available

in generic forms and long-documented to safely and effectively lower LDL-C levels and CVD risk.

For secondary prevention in people who have already had a myocardial infarction (MI) or stroke and are at highest risk for a recurrence and whose LDL-cholesterol levels are not adequately lowered by statin therapy, the guidelines now recommend the select use of other cholesterol-lowering drugs that can be added to a statin regimen. The guidelines recommend a graded approach with ezetimibe, which is now available as a generic, in addition to the statin for these patients. If that combination is not sufficiently effective, a PCSK9 inhibitor could be added, specifically for people who are at very high risk.⁶ This approach may also be considered in primary prevention for people who have familial hypercholesterolemia. Once treatment is started, whether only lifestyle modifications are prescribed or if medication therapy is added, adherence and efficacy should be assessed at 4-12 weeks with a fasting lipid test, subsequently retested every 3-12 months as needed.

As mentioned, another new aspect of the guidelines is the recommendation of coronary artery calcium (CAC) measurements for people in some risk categories. A CAC score of zero typically indicates a low risk for CVD and could mean those people can forego or at least delay cholesterol-lowering therapy as long as they are non-smokers or do not have other high-risk features.

Pediatric Population

Recognizing the cumulative effect of high cholesterol over long-term and over the full lifespan of an individual, identifying and treating it early can help reduce the lifetime risk for CVD. Selective cholesterol testing is appropriate for children as young as 2-years old who have a family history of heart disease or high cholesterol. As mentioned, in most children, an initial test can be considered between the ages of 9 and 11 and then again between 17 and 21. Because of a lack of sufficient evidence in young adults, there are no specific treatment recommendations for that age group. However, it is essential that they adhere to a healthy lifestyle, be aware of the risk of high cholesterol levels and receive therapy as appropriate at all ages to reduce the lifetime risk of CVD and stroke. When high cholesterol is identified in children (**Table 4**), that could also alert a physician to test other family members who may not be aware that they have high cholesterol levels; awareness and treatment can save lives. Finally, the guidelines offer more specific recommendations for certain age and ethnic groups, as well as for people with DM, all important for the comprehensive and individualized medical provider-patient discussion approach.

Table 4. Lipid values in children (mg/dl)
Acceptable / Borderline/Abnormal

Total cholesterol	<170 / 170-200 / >200
Triglycerides	
Age 0-9 y	<75 / 75-100 / >100
Age 10-19 y	<90 / 90-130 / >130
HDL cholesterol	>45 / 40-45 / <40
LDL cholesterol	<110 / 110-130 / >130
Non-HDL cholesterol	<120 / 120-145 / >145

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