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REVIEW ARTICLE

New 2018 ACC/AHA Guidelines on Cholesterol Management: Key Changes and Implications

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During the American Heart Association (AHA)'s scientific sessions held in November 2018, the new ultisociety Guideline on the Management of Blood Cholesterol[1] was presented to the cardiology community emphasizing some previous key recommendations and new concepts in atherosclerotic cardiovascular disease (ASCVD) prevention. The main updates of these guidelines are:

1) a new 10-y risk ASCVD categorization for adults 40 to 75 years of age and a lifetime risk estimation in young patients;

2) upgrading of non-statin therapies for LDL-cholesterol lowering treatment;

3) use of LDL-c thresholds (and not only of percental reduction) to consider intensification of therapy;

4) time of blood collection to measure lipid levels;

5) inclusion of the coronary artery calcium (CAC) score in the decision-making process in the management of intermediate-risk patients.

A healthy lifestyle including an anti-atherogenic diet, physical activity, weight control and not smoking remains the cornerstone for cardiovascular prevention. Regardless of pharmacological treatment used, these habits are important at all ages, and are some of the key recommendations for ASCVD prevention.

About the treatment with lipid-lowering drugs, statins remain as the first-choice agents. However, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have gained attention as add-on drugs in a more aggressive approach for low-density lipoprotein cholesterol (LDL-c) reduction. Ezetimibe, a cholesterol absorption inhibitor, is the most commonly used drug in combination with statins, contributing for an additional 15-30% reduction in LDL-c levels.

Considerable changes have been made in lipid-lowering therapy with the use of monoclonal antibodies that inhibit PCSK9, such as evolocumab and alirocumab. Based on studies showing an 1.5% absolute risk reduction in composite ASCVD outcomes in a follow-up of 2.2-2.8 years, these new drugs are now recommended and should be included to therapy if lipid targets are not met after maximally tolerated doses of statin and ezetimibe. Recommendations are detailed below:

- Established ASCVD: high-intensity statin should be indicated aiming at a ≥ 50% LDL-c reduction (and LDL-c < 70 mg/dl in those at very high ASCVD risk – Table 1). If this target is not achieved, ezetimibe should be added followed by PSCK9 inhibitors. The rationale is based on the findings that support the safety of extremely low LDL levels, and that, for LDL-c levels, "lower is better".[2]

- Primary prevention (Figure 1)

- 10-year ASCVD risk calculation: the 10-y risk of ASCVD (calculated by the pooled cohort equation - PCE) is now categorized as:

a. low (< 5%) – lifestyle changes are indicated;

b. borderline (5% –< 7.5%) – the initiation of moderate-intensity statin therapy is recommended in selected cases;

c. intermediate (7.5% –< 20%) – this is one of the main updates of the guideline. In the presence of risk-enhancing factors, it is suggested to start a moderate-intensity statin in this new group (Table 2). In addition, if the need for statin therapy by the patient remains uncertain (a common situation), the CAC score may

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Table 1 - Established ASCVD and High-Risk Factors

Major ASCVD
ACS within the past 12 months
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease
High-Risk Conditions
Age ≥ 65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dl) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

ABI: indicates ankle-brachial index; ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; LDL: low-density lipoprotein cholesterol; and MI, myocardial infarction.

be a reasonable tool for assessing the risk of ASCVD in these patients. Since the CAC score is the tool that best adds predictive value of cardiovascular outcomes to risk calculators,[3] its use is recommended by the most recent guidelines when drug treatment is not well defined.

Thus, in case of a CAC score of 1 to 99 Agatston units, introduction of pharmacological therapy should be individualized, particularly in those ≥ 55 years of age.[4] Also, in any patient with CAC ≥ 100 Agatston or ≥ 75th percentile (regardless of the CAC score), statin therapy should be introduced. On the other hand, in individuals with a CAC of zero, statin therapy may be withheld or delayed, considering the very low incidence of cardiovascular events observed in this population.[5]

d. high risk (≥ 20%) – as recommended in the previous statement, high-intensity statin is indicated aiming at reducing LDL-c levels by ≥50%.

- Specific Situations

- Severe hypercholesterolemia (LDL-c ≥190 mg/dl): high-intensity statins are indicated, with not need for risk calculation. Ezetimibe should be added if LDL-c reduction is ≤ 50% or remains ≥ 100 mg/dl. This group, composed mostly of people with familial hypercholesterolemia, received special attention due to the high rate of cardiovascular events, corresponding to 3-4-fold higher risk compared with other individuals with the same LDL-c levels.

- Diabetes: patients aged 40-75 years old with diabetes should be treated with moderate-intensity statin and, in case of a 10-y ASCVD risk ≥ 20%, high-intensity statin should be added.

These updated recommendations highlight a more personalized approach, with a follow-up of lipid profile for up to 20 years-old, with reassessment every 4-6 years. If pharmacological therapy is implemented, a closer follow-up is recommended to check LDL-c levels, safety and adherence. Regarding young adults (20 to 39 years of age), it is crucial to exclude secondary causes of hypercholesterolemia, as hypothyroidism (TSH), obstructive liver disease, renal disease and nephrosis, as well as dietary and medication-related dyslipidemia. Also, as mentioned before, intensive lifestyle change is strongly indicated due to its potential to reduce ASCVD risk. For young adults with persistent hypercholesterolemia (LDL-c levels above 160-189 mg/dL), it is recommended to consider risk-enhancing factors in the decision on whether to prescribe statins. For all patients with LDL-c ≥ 190 mg/dl, treatment should be conducted as previously described in "severe hypercholesterolemia" section.

Lifestyle therapies are also pivotal in the management of children and adolescents with abnormal lipid values, aiming to treat obesity and other ASCVD risk factors. Also, this helps to identify individuals who would clearly benefit from statins,6 especially among those with persistent LDL-c ≥ 190 mg/dl (or LDL-c ≥ 160 mg/dl with familial hypercholesterolemia). Due to the very early atherogenic process in familial hypercholesterolemia, children and adolescents with a family history of early ASCVD or severe hypercholesterolemia should be evaluated for lipid profile as early as age of 2 years. Once hypercholesterolemia is detected, a comprehensive family screening is recommended to detect familial forms of hypercholesterolemia.

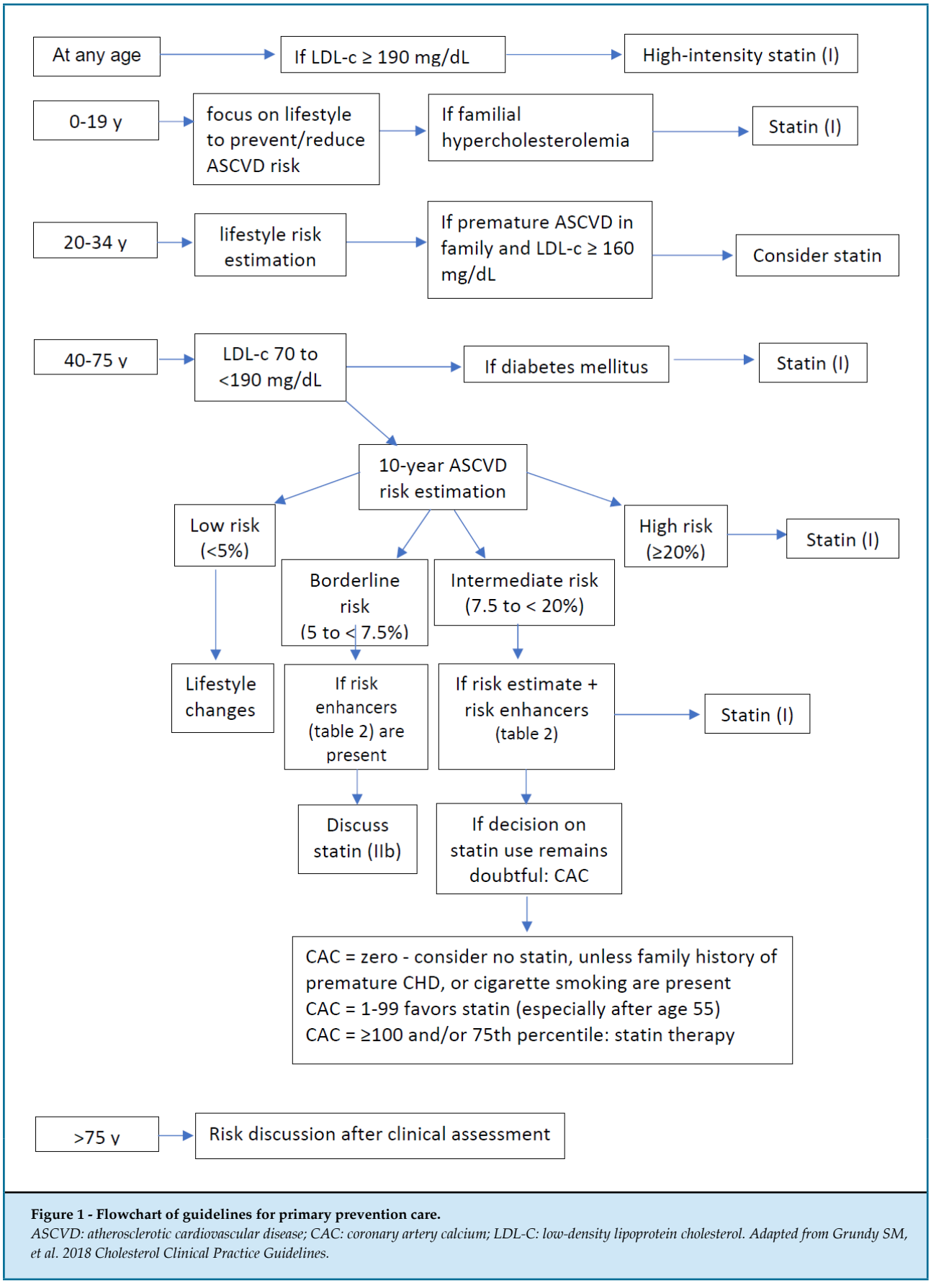

Figure 1 - Flowchart of guidelines for primary prevention care.
ASCVD: atherosclerotic cardiovascular disease; CAC: coronary artery calcium; LDL-C: low-density lipoprotein cholesterol. Adapted from Grundy SM, et al. 2018 Cholesterol Clinical Practice Guidelines.

Table 2 - Risk-Enhancing Factors

- Family history of premature ASCVD - (men < 55 years; women < 65 years)
- Primary hypercholesterolemia (LDL-C 160-189 mg/dl; non-HDL-C 190-219 mg/dl
- Metabolic syndrome
- Chronic kidney disease (eGFR 15- 59 ml/min per 1.73 m^2)
- Chronic inflammatory conditions: psoriasis, rheumatoid arthritis (RA) or human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)
- History of premature menopause (before age 40) and history pre-eclampsia at pregnancy
- High-risk ethnicities (e.g. South Asian)
- Lipid/Biomarkers:
  a. Persistently elevated, primary hypertriglyceridemia (≥ 175 mg/dl);
  b. If measured:
    - High-sensitivity C-reactive protein ≥ 2.0 mg/L
    - Lp(a) ≥ 50 mg/dL or ≥ 125 nmol/L
    - Apo B ≥ 130 mg/dL
    - ABI < 0.9

AIDS: acquired immunodeficiency syndrome; ABI: ankle-brachial index; apoB: apolipoprotein B; ASCVD: atherosclerotic cardiovascular disease; eGFR: estimated glomerular filtration rate; HDL-c: high-density lipoprotein cholesterol; HIV: human immunodeficiency virus; LDL-c: low-density lipoprotein cholesterol; Lp(a): lipoprotein (a); and RA: rheumatoid arthritis.

In conclusion, even though the clinical risk stratification followed by selective use of preventative pharmacological interventions is still the main strategy of primary prevention, these new guidelines allow individualization of treatment by complementary risk stratification, new therapies and facilitation of patient involvement in a shared decision making process.

Author contributions

Conception and design of the research: Generoso G, Bittencourt MS. Acquisition of data: Generoso G, Bittencourt MS. Analysis and interpretation of the data: Generoso G, Bittencourt MS. Writing of the manuscript: Generoso G, Bittencourt MS. Critical revision of the manuscript for intellectual content: Generoso G, Bittencourt MS.

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