NEW 2019 ESC/EAS GUIDELINES FOR THE MANAGEMENT OF DYSLIPIDEMIAS

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Keywords: *cholesterol; dyslipidemia; guidelines; total cardiovascular risk; treatment*

During the 2019 European Society of Cardiology (ESC) congress, on August 31, the new guidelines for the management of dyslipidemias were released, which were simultaneously published online in the *European Heart Journal*.[1]

Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.[2] Professional guidelines are important because they provide a practical and ethical framework for decision-making and because they instill a sense of responsibility and accountability. The Members of the Task Force for the management of dyslipidemias of the ESC and European Atherosclerosis Society (EAS), including professionals involved with different aspects of the medical care of patients with dyslipidemias, undertook a comprehensive review of the published evidence in this field, with the aim of updating the previous ESC/EAS lipid guidelines published in 2016.[3]

A recently published EAS consensus statement,[4] based on evidence from genetic studies, epidemiological studies, Mendelian randomization studies, and randomized clinical trials, clearly showed the causal role for low-density lipoprotein cholesterol (LDL-C) and other cholesterol-rich apolipoprotein B–containing lipoproteins in atherogenesis. This implies that targeting elevated LDL-C, and doing it as soon as possible, will have greater benefit in terms of cardiovascular prevention.

Another crucial point is the focus on total cardiovascular risk, as explained in the title of the guidelines "lipid modification to reduce cardiovascular risk."[1] The new guidelines recommend a lifetime approach to cardiovascular risk, implying that people of all ages should be encouraged to adopt or sustain a healthy lifestyle, and the customization of the lipid management approach, stratifying the patients into risk categories, each with a specific therapeutic goal:

- **For patients at very-high risk** (people with documented atherosclerotic cardiovascular disease [ASCVD], diabetes mellitus with target organ damage or at

least three major risk factors, severe chronic kidney disease, familial hypercholesterolemia with ASCVD or with another major risk factor, or a 10-year risk of cardiovascular death >10%), an LDL-C reduction of at least 50% from baseline and an LDL-C goal of less than 1.4 mmol/L (<55 mg/dL) are recommended. For very high-risk patients who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of less than 1.0 mmol/L (<40 mg/dL) is recommended.

- **For patients at high risk** (people with markedly elevated single risk factors, familial hypercholesterolemia without other major risk factors, diabetes mellitus without target organ damage, moderate chronic kidney disease, or 10-year risk for cardiovascular death of 5% to 10%), an LDL-C reduction of 50% or greater from baseline and an LDL-C goal of less than 1.8 mmol/L (<70 mg/dL) are recommended.
- **For individuals at moderate risk** (diabetic patients with a duration of diabetes mellitus <10 years and no others risk factors, 10-year risk for cardiovascular death of 1% to 5%), an LDL-C goal of less than 2.6 mmol/L (<100 mg/dL) should be considered.
- **For individuals at low risk** (10-year risk for cardiovascular death <1%), an LDL-C goal of less than 3.0 mmol/L (<116 mg/dL) may be considered.

The guidelines also introduce the recommendation of using new tests to stratify risk among moderate-risk patients. These tests include both coronary artery calcium imaging and biomarker tests. Coronary artery calcium score assessment may be helpful in people who are at moderate risk of ASCVD, informing discussions about treatment strategies in untreated patients not at their LDL-C goal. Likewise, assessment of arterial (carotid or femoral) plaque burden on ultrasonography may be informative. As concerns biomarkers, the use of apolipoprotein B may help in risk stratification in people where the measurement of LDL-C underestimates atherosclerotic burden (eg, in case of high triglycerides, diabetes mellitus, obesity, or very low LDL-C), as it recapitulates individual exposure to proatherogenic lipoproteins. Moreover, a measurement of Lp(a) (once in life) may be helpful for further risk stratification of patients at high risk of ASCVD or in patients with a family history of premature cardiovascular disease, besides the identification of people with very high inherited Lp(a) levels and so potentially at a higher ASCVD risk.

The key message of these guidelines, which has been carried forward from the previous edition and emphasized in this new version, is “the lower the better” in terms of reducing LDL-C. This emerges as two main novelties. First, these guidelines proposed more ambitious LDL-C goals, especially for high- and very-

high-risk patients. Second, for patients at high or very-high risk, a 50% reduction in the basal LDL-C is recommended, as has been derived from the previous guidelines, which has significant implications. For example, patients at very-high risk now have a recommended LDL-C goal of 1.4 mmol/L and at least a 50% reduction from baseline levels. If a patient at very-high risk has an untreated LDL-C level of 1.5 mmol/L, which is just above the goal, then the recommendation of needing a 50% reduction would require LDL to be further lowered to 0.75 mmol/L. At the same time, a patient with very high LDL-C levels (such as familial hypercholesterolemia) will also have, in addition to reaching the 50% reduction, to attempt to reach the goal level. The rational for this approach is the increasingly confirmed evidence that the risk reduction is directly proportional to the magnitude of LDL-C lowering. Therefore, an optimal reduction in risk is secondary to a maximized LDL-C reduction.

The new guidelines recommend that patients be treated aggressively with high-dose statins and with the option of adding ezetimibe, and as third-line, a proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitor, to achieve these goals. These changes from the 2016 document are based on several recent placebo-controlled clinical studies, which have shown that the addition of either ezetimibe or anti-PCSK-9 monoclonal antibodies to statin therapy provides a further reduction in ASCVD risk, proportional to the absolute LDL-C reduction. These studies have clearly indicated that the lower the achieved LDL-C values, the lower the risk of future cardiovascular events, with no lower limit for LDL-C values. In addition, studies to date have shown that reaching very low LDL-C values has no significant safety implications.

As stated in the preamble of the 2019 document, the "guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition."[1] However, it is important to remember that the final decisions concerning an individual patient must be made by the responsible health professional(s), sharing the approach with patients (and their relatives, when appropriate) and taking into account their expectations and preferences, if feasible. Statins are very well tolerated, and true "statin intolerance" is uncommon, although patients often reported discomfort or muscle pains, and practitioners might find this difficult to manage. Several studies have shown a considerable LDL-C–lowering effect of alternative dosing, such as every other day or twice a week. When it is necessary to reduce the dose or discontinue statin therapy, ezetimibe and PCSK-9 inhibitors are effective treatment options to achieve the lipid goals. Notably, the guidelines clearly state that statins are not recommended in premenopausal women considering pregnancy or not using adequate contraception. In addition, the evidence for statin therapy is more limited in patients over 75, though it is still consistent

with a benefit. The guidelines advise taking the level of risk, baseline LDL-C levels, health status, and the risk of drug interactions into account before starting statin therapy in elderly people.

Finally, the patient's perspective should also be taken into account, trying to promote the adoption of healthy lifestyle changes and to maximize adherence to therapy. Practitioners should adequately motivate the patients, providing them with all the information necessary to understand the importance of cardiovascular prevention and the possible need for lifestyle and pharmacological interventions. When necessary, self-care by the patient should be facilitated, using written instructions (or electronic tools, where appropriate), simplifying the drug regimen, and possibly actively involving family members. ■

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