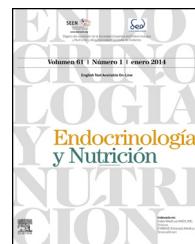# ENDOCRINOLOGÍA Y NUTRICIÓN

EDITORIAL

Statin-centered treatment of dyslipidemia. New evidence-based paradigm, or only part of the evidence?[☆]

Tratamiento estatino-céntrico de la dislipemia. ¿Nuevo paradigma basado en la evidencia o solo parte de la evidencia?

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The updated guidelines of the American College of Cardiology/American Heart Association (ACC/AHA)[1] show a change in the paradigm for the treatment of hypercholesterolemia, as they renounce the treatment goal in low density lipoprotein cholesterol (LDL-C) levels in order to focus on the clinical benefits of statins, establishing the use of a specific statin preparation and dose as the objective. This has raised multiple questions and comments regarding the contents of the guidelines and their application in different countries, including Spain.[2–6] The contents I consider most controversial in respect of their application in a clinical setting are discussed below.

These guidelines are intended to simplify the control of blood cholesterol by identifying specific subgroups of patients who would benefit from statin therapy (atherosclerotic cardiovascular disease, LDL-C levels $\geq$190 mg/dL, or a history of type 1 or 2 diabetes mellitus). The guidelines prioritize these three groups based on the evidence from controlled clinical trials. For the rest of the population aged 40–75 years not included in any of these groups who have LDL-C levels ranging from 70 to 189 mg/dL, it

is recommended that 10-year cardiovascular risk be estimated based on the traditional risk factors using the new tables based on the Pooled Cohort Equations and developed by the Risk Assessment Work Group along with data from previous studies. However, this attempt at simplification leaves out different groups of patients with clear differential characteristics. In this regard, the management of people older than 75 years and younger than 40 years of age with high cardiovascular risk is particularly significant in this regard. On the other hand, there is some concern and debate regarding the overestimation of risk with the proposed equation because it is thought that it has not been sufficiently tested and validated, and that it does not represent an advance as compared to other equations such as the Score, widely used and more applicable in Europe.[2–4]

The ACC/AHA guidelines provide a classification of the different statins and doses based on their potential to lower LDL-C levels, so facilitating the selection of the preferred type of statin, and of the adequate dosage based on individual risk. This should be considered a positive aspect of the guidelines because the treatment of dyslipidemia is based on the use of statins as the lipid-lowering drugs of choice due to their efficacy in decreasing cardiovascular morbidity and mortality, which is proportional to the reduction of plasma cholesterol levels.[7] However, the guidelines do not contemplate the use of other additional lipid-lowering drugs and ignore the residual lipid risk in statin-treated patients.

This is a relevant issue because some patients have a poor response to statins and approximately 10–20% of patients do not tolerate them. Because of these and other factors, LDL-C goals are not achieved in up to 40% of patients. Thus, despite the unquestionable efficacy of statins, additional drugs as monotherapy and in combination with statins are required in many patients to prevent and treat cardiovascular diseases. In the SHARP study,[8] the combination of statin and ezetimibe decreased event rates in subjects with chronic kidney failure, and the IMPROVE-IT study confirmed that the combination of ezetimibe and statin provided an additional LDL-C decrease which was associated with a significant reduction in ischemic coronary and cerebrovascular episodes in patients with acute coronary syndrome.[9] In addition, it showed that the benefits associated with decreased LDL-C levels were continuous and persisted up to at least 53 mg/dL. Finally, in the FIELD and ACCORD studies, analyses of subgroups with elevated triglyceride levels and low HDL-C levels suggested the efficacy of treatment with fenofibrate, and the VA-HIT study showed vascular event reduction with gemfibrozil treatment.

The most important change in the ACC/AHA guidelines is the replacement of explicit treatment goals (LDL-C levels) by statin therapy treatment of different intensities based on risk stratification. The measurement of LDL-C levels is only recommended before drug treatment is started and at 4–12 weeks to assess if the extent of the reduction is consistent with the potency of the statin used. The reasoning behind this change is that most interventional studies with statins have used a fixed dose, with no titration, to achieve a specific LDL-C or non-HDL cholesterol goal, and that the benefits of achieving two different therapeutic LDL-C goals have not been compared either. Although these data are unquestionable, the additional genetic and epidemiological evidence available, as well as evidence from observational and interventional studies, shows a linear relationship between LDL-C levels and cardiovascular risk.[10,11] Finally, the results of the IMPROVE-IT study[9] support the concept of ''the lower the better'' for LDL-C, in contrast to the theory of ''the higher the better'' regarding the intensity of statin treatment. All these data support the maintenance of the therapeutic LDL-C goal. On the other hand, this change in paradigm to one that does not require control laboratory tests, may have a negative impact on patients and physicians.[4] Physicians in general, and especially endocrinologists, are used to a working method based on widely agreed control goals, and find it difficult to treat blindly, while patients have a perception of less follow-up and control when their treatment is not monitored. The measurement of LDL-C levels and other lipid parameters provides an indication concerning patient adherence and individual response to a given statin dose, and leaves the door open for combination therapy in patients in whom it is considered to be indicated.

As noted above, the guiding spirit behind these new guidelines is that it is based on so-called level[1] evidence or high level evidence, which includes randomized clinical trials (RCTs), systematic reviews, and meta-analyses. However, this procedure is also its main limitation, because it involves the limitations derived from RCTs, including the selection of participants and the unusual follow-up of the study population during the duration of the clinical trial. No consideration has been given to the contributions of decades of knowledge based on biochemical and genetic studies, or epidemiological, observational and animal experimental studies, amongst others, which served to design RCTs and help interpret and apply the direct information provided by RCTs. Thus, taking into account that the evidence derived from RCTs is only part of the evidence, that there are no RCTs available for each clinical setting, and that the lack of evidence from RCTs does not indicate lack of benefit, non-consideration of the information derived from studies other than RCTs restricts the reasoning required for decision making in each individual patient, making the practice of medicine a rigid process which is unsatisfactory and predictably less efficient.

Looking forward to future guidelines that consider ''the full evidence'', it is my belief that the management of dyslipidemia should be individualized, with the information provided by RCTs being taken into account when deciding on a clinical approach, but that this clinical approach should also be based on all the available evidence and on experience. When starting therapy, overall risk, lipid levels, and the fact that the concept ''the lower the better'' for LDL-C probably continues to be valid for many patients should all be taken into account. In this context, high-risk patients should receive high-intensity statin therapy or high-intensity cholesterol-lowering therapy with statins plus ezetimibe, and levels of LDL-C and other lipids should be monitored to ensure compliance and to adjust statin doses or to add other lipid-lowering drugs if needed.

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