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Editorial

Comments on the 2011 ESC/EAS guidelines for the management of dyslipidemias. A report of the Task Force of the Clinical Practice Guidelines Committee of the Spanish Society of Cardiology

Comentarios a las guías de práctica clínica sobre manejo de las dislipemias de la Sociedad Europea de Cardiología y la Sociedad Europea de Aterosclerosis 2011. Un informe del Grupo de Trabajo del Comité de Guías de Práctica Clínica de la Sociedad Española de Cardiología

SEC Task force for dyslipidaemia guidance: Manuel Anguita * (coordinator), Eduardo Alegría, Vivencio Barrios, José A. Casasnovas, Carlos Escobar, Monserrat León, Emilio Luengo, and José L. Llisterri

Clinical Practice Guidelines Committee of the SEC: Ángel Alonso, Ángel Cequier, Josep Comín, Antonio Fernández-Ortiz, Magda Heras, Manuel Pan, and Fernando Worner

Document revisers: Gonzalo Barón, Eva Bernal, Xavier Borrás, Fernando Civeira, Alberto Cordero, Eliseo Guallar, Borja Ibáñez, Martín Laclaustra, Carmen de Pablo, Domingo Pascual, Tomás Ripoll, Ginés Sanz, and Silvia Serrano

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INTRODUCTION

In line with the new philosophy on clinical practice guidelines adopted by the executive committee of the *Sociedad Española de Cardiología* (SEC: Spanish Society of Cardiology), which was explained and justified in a recent document published in the *Revista Española de Cardiología* (REC),[1] this article has the objective of discussing the most important and novel aspects of the guidelines on the management of dyslipidemias but without attempting to replace them. A joint effort by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS),[2] these guidelines updated the old protocols for treating dyslipidemias developed by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP III) and published in 2001 (summary) and 2002 (complete text),[3] with a minor update in 2004.[4] In Spain, recommendations from the *Comité Español Interdisciplinario para la Prevención Cardiovascular* (CEIPC) have been used more recently,[5] with the approval of the Spain's Health Ministry and the participation of the SEC, although in this Spanish guideline dyslipidemia is just one section of the general recommendations on cardiovascular prevention.

METHODS

The clinical practice guidelines committee of the SEC formed a task force made up of clinical cardiologists, primary health care providers, and experts in lipids and cardiovascular risk recommended by the SEC sections on clinical cardiology and on preventive cardiology and rehabilitation, with the general objective of reviewing the evidence and recommendations provided by the previously mentioned European guidelines on dyslipidemias,[2] accepted by the SEC and published in REC.[6] These doctors were asked to analyze the guidelines using a basic questionnaire that served as a reference method to homogenize the information provided. This questionnaire included the following points: *a)* comments on the characteristics and applicability of the ESC guidelines; *b)* an analysis of the methodology of the guidelines; *c)* novel/most important contributions to clinical practice; *d)* an analysis of the most positive and most questionable aspects of these novel contributions and a comparison with other guidelines on the subject; *e)* deficient aspects of the guidelines, and *f)* conclusions and implications for clinical practice in our country. With the comments from these experts, we developed a consensus document that was approved by all of the members of the task force. This document was sent for review to another group of 13 experts proposed by the scientific sections of clinical cardiology and rehabilitation and preventative cardiology, whose comments were

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*Corresponding author: *Comité de Guías de Práctica Clínica*, *Sociedad Española de Cardiología*, Madrid, y *Servicio de Cardiología*, *Hospital Reina Sofía*, Avda. Menendez Pidal s/n, 14004 Córdoba, Spain.
E-mail address: manuelp.anguita.sspa@juntadeandalucia.es (M. Anguita).

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Table 1
Recommendations From the European Guidelines for the Management of Dyslipidemias, Organized by the Class of the Recommendation and Level of Evidence Given

Class	Level of evidence	Number of recommendations	Class	Number of recommendations	Level of evidence	Number of recommendations
I	A	15	I	51	A	28
	B	4				
	C	32				
IIa	A	12	IIa	34	B	19
	B	9				
	C	13				
IIb	A	0	IIb	12	C	55
	B	5				
	C	7				
III	A	1	III	5		
	B	1				
	C	3				

integrated into the final document. We asked for a declaration of conflicts of interest in relation to this subject from each member, which is detailed at the end of this article.

GENERAL COMMENTS AND ANALYSIS OF METHODOLOGY

The ESC decided at one point that the protocols for clinical practice should adopt the format of articles that could be published in the European Heart Journal (with the consequent supplementary material available on the electronic webpage of the ESC, as well as other supporting formats such as leaflets, cards, etc.). This has caused space problems that inhibit a detailed description of the methodology. In these guidelines, as in previous versions from the ESC, the familiar format is used for I, IIa, IIb, and III indications (with their corresponding A, B, and C levels of supporting evidence). All of the summary tables have the same general structure: *a)* causes and indications listed in the guidelines; *b)* grade or category of the indication (I, IIa, IIb, or III-contraindication), and *c)* level of evidence for the indication (A, B, or C). The reiterated and systematic order of this table structure allows for easy use in normal clinical practice. These guidelines make a total of 102 recommendations (without taking into account the relative impact of lifestyle changes on lipid parameters). As shown in Table 1, the majority of recommendations are type I or IIa. However, approximately 50% of the recommendations are based on expert consensus (level C evidence). The predominance of level C evidence in almost all of the tables represents a weakness derived from the lack of relevant studies. This excess of level C evidence, which is not exclusive to European guidelines, may possibly be due to the intention of covering all possible situations, and perhaps it would be better to avoid such a high number of expert personal opinions and only highlight those that have clearly demonstrated supporting evidence. This would produce "minimum" guidelines with indisputable recommendations that have greater power behind them. The guidelines should also point out existing information gaps and propose well-designed studies in order to fill them.

Logically, the guidelines summarize the well-founded evidence available and is quite conservative in exploring diagnostic and therapeutic processes that are particularly novel or have a lack of supporting evidence, which are only mentioned and not given in-depth analysis. It is also conservative in the sense of faithfully holding to the evaluation standards utilized by large studies with regard to the treatment of dyslipidemias: the control of cardiovascular risk is orientated through the treatment of dyslipidemias. The methodology used to compose the guidelines holds certain interest because it approaches the problem from the point of view of the diseases and their risks (eg, lipid alterations), and in the context of the different pharmacological groups implicated.[2] As expected, besides the expectations for the guidelines before their publication the document has produced both positive and negative reactions. In any case, the new European guidelines are intended to replace previous publications, and it is likely that this will occur, as we discuss below.

RELEVANT AND/OR NOVEL ASPECTS

The most important and/or novel aspects identified by the task force are the following:

1. The treatment of dyslipidemia should not be considered as an isolated process, but rather within the context of integrated prevention of cardiovascular disease in each patient. The SCORE scale is recommended as a basic tool for calculating cardiovascular risk.

2. Therapeutic objectives: strengthening of strict low-density lipoprotein cholesterol (LDLc) targets for patients with very high, high, and intermediate risk levels (no longer an optional criterion).

3. Nonpharmacological therapies: the relevance of diet and exercise not just in the reduction of total risk, but also in the specific treatment of dyslipidemias.

4. Lipid-lowering drugs: a logical emphasis on statins as an essential treatment for cardiovascular prevention, and scarce detail on fibrates, niacin, and absorption inhibitors.

5. Dyslipidemia treatment in special clinical situations: the detailed description of targets and prescriptions in several situations and subgroups.

CRITICAL EVALUATION OF RELEVANT AND/OR NOVEL ASPECTS

1. Evaluation of Total Cardiovascular Risk Using the SCORE Scale

The new guidelines recommend stratifying total risk using the SCORE risk table.[7] According to this scale, patients can be classified as having very high, high, moderate, or low cardiovascular risk. The preference for the SCORE system over other risk scales is based on the fact that it was designed and evaluated using representative European cohorts.[8] The SCORE scale allows for estimating the 10-year risk of the first lethal atherosclerotic complication based on the following risk factors: age, sex, tobacco use, systolic blood pressure, and total cholesterol. Different tables are available for high and low risk areas of Europe as well as for each sex. Based on the patient's background and current risk factors, the recommended risk classification system in these European protocols is more simple and practical than in others: patients with a documented background of cardiovascular disease, type 2 diabetes mellitus (DM) or type 1 with organ damage (e.g., microalbuminuria), moderate or advanced chronic renal failure, and those with a SCORE risk calculation >10% are automatically

Table 2
Target Cholesterol Control Values for Low-Density Lipoproteins According to the European Guidelines for the Management of Dyslipidemias

Type of patient	Target	Recommendation	Supporting studies
Very high risk	< 70 mg/dl (1,8 mmol/l)	I (A)	Refs. 12, 13 and 14
High risk	< 100 mg/dl (2,5 mmol/l)	IIa (A)	Refs. 12, 15 and 16
Moderate risk	< 115 mg/dl (3,0 mmol/l)	IIa (C)	?
Low risk	?	?	?

The terms "very high risk," "high risk," "moderate risk," and "low risk" are derived from the SCORE scale and are explained in the text.

classified as having very high cardiovascular risk. In all other cases, the SCORE scale is recommended for estimating the risk of cardiovascular death (high, 5%-10%; moderate, 1%-5%; and low, <1%) (Table 2). Another element to highlight is the inclusion of high-density lipoprotein cholesterol (HDLc) measurements in the SCORE calculation of risk, which recognizes the role these molecules play in the biopathology of cardiovascular disease (CVD).[7]

The primary advantage in using the SCORE table is that it is designed specifically for the European population; in particular, the low-risk table is applicable to the Spanish population. Additionally, keeping in mind the particularities of HDLc in Spain, the adjusted tables for HDLc in the supplementary material are especially useful. Since the primary determining factor for cardiovascular risk is age, a relative risk table is recommended for use in the young population. Although the absolute SCORE risk can be low in young patients, if several risk factors are present, the relative risk will be high.

The SCORE scale is not without its flaws. For example, it does not reflect how the presence of metabolic syndrome or conditions such as left ventricular hypertrophy or microalbuminuria affect risk stratification. These are not quantified in the dyslipidemia guidelines, although the European guidelines for arterial hypertension state that these patients do have cardiovascular risk when blood pressure is ≥130/85mm Hg.[9] In SCORE, age is very important, which means that elderly patients are deemed at high risk even in the absence of other risk factors or associated diseases. It is unknown whether the same targets for patient control should be maintained in this context. An interesting and positive addition in the new guidelines is the inclusion of patients with moderate to severe deteriorated renal function in the category of very high cardiovascular risk.[10] However, since age is associated with a physiological loss of renal function, perhaps glomerular filtration rate should be adjusted based on age. Otherwise, the majority of patients aged >65 years would have a target LDLc<70 mg/dl even in the absence of any other associated risk factor or disease. In other words, the number of people aged >65 years considered as candidates would be overestimated.[11] On the other side of the age spectrum, even in the presence of several risk factors, the absolute risk of death for a 10-year-old is very low. For this reason, the relative risk table (Figure 3 in the guidelines) should be used in the case of young patients. In a young patient with multiple risk factors, even with a low absolute risk of cardiovascular death at 10 years, the relative risk as compared to other subjects of the same age can still be high. The SCORE table was created by analyzing European populations; as a result, we are unsure whether these guidelines would only be applicable in Europe as opposed to, for example, the guidelines for arterial hypertension,[9] which are widely used throughout the world. Although it is mentioned briefly in the general document, the supplementary material lacks a table that compares the SCORE system with the Framingham criteria, among others.

In conclusion, despite these doubts, and per recommendation by the ESC/EAS guidelines, the SCORE scale, with the specific considerations described, is probably a good tool for evaluating individual cardiovascular risk in Europe and therefore in the Spanish population.

2. Treatment Objectives

The new guidelines continue to recognize that elevated levels of total cholesterol and LDLc are the most important dyslipidemia in terms of prognosis as well as quantity of available epidemiologic, pathologic, and therapeutic data exist. Other dyslipidemias are also discussed, however briefly, that predispose the patient to premature coronary disease, such as the atherogenic lipid triad, in which very low density lipoproteins are elevated and which is expressed by a moderate elevation of plasma levels of triglycerides and LDLc, with reduced levels of HDLc. An extrapolation of the available data shows that an absolute reduction in LDLc to values <70 mg/dl, or a relative reduction of 50% from initial values, provides a greater benefit in terms of CVD prevention. As such, this is the target in patients with very high risk and it is not considered optional, as it was in the NCEP-ATP III protocols.[4] Stricter LDLc targets have also been developed for high-risk (<100 mg/dl) and moderate-risk (<115 mg/dl) patients, although these recommendations are based solely on expert consensus. The guidelines no longer differentiate between threshold concentrations for starting nonpharmacological or pharmacological treatment, as well as recommended and special target concentrations. Both HDLc and apolipoprotein B (ApoB) can be considered as possible treatment targets, especially in patients with type 2 DM, metabolic syndrome, or combined dyslipidemia.

Table 2 summarizes these recommendations and the evidence used to support them.[12-16] Clear evidence exists for the recommendations given in the case of patients with high or very high risk, but not for the moderate-risk group, with no explanation in the text. With the target of <115 mg/dl, it is possible that some patients may be prescribed statins when lifestyle changes would be sufficient. Additionally, low-risk patients have no recommendations for treatment goals. Surprisingly, Table 8 from the guidelines does not include such recommendations, although Table 3 does suggest lifestyle changes for low-risk patients with LDLc >100 mg/dl, and recommends considering statins when LDLc >190 mg/dl. In this low-risk population, the question is whether to follow the ATP III targets (<160 mg/dl)[4] or the recommendation given by the 2007 cardiovascular risk prevention guidelines (<115 mg/dl).[17]

On the other hand, it may surprise that the guidelines do not excessively state target cholesterol levels, nor have they delved seriously into markers other than the traditionally used LDLc, HDLc, triglycerides, and total cholesterol. However, this is justified since not all analytical laboratories in Europe (which is the natural scope of the guidelines) possess the necessary technology for making PCRas, ApoB, ApoA-I, direct LDLc, and other complex analytical measurements on a regular basis. Additionally, the majority of these laboratory analyses have a significantly lower evidence level than the commonly used metrics. The therapeutic targets for LDLc differ from those in other guidelines. For low-risk patients, the Canadian

guideline[18] recommends reducing LDLc by at least 50%, although it does not establish a concrete value. For high- and moderate-risk patients, the target is the same. The ATP III[4] sets different targets for patients at different risk levels: high, <100 mg/dl (optional, 70 mg/dl); moderate-high, <130 mg/dl; moderate, <160 mg/dl; and low, <160 mg/dl.

Another arguable aspect is that the guidelines recommend, above all and in a very specific manner, interventions in patients with clinical CVD or high risk, which equates to indicating lipid-lowering drugs in patients with advanced vascular damage, and yet interventions are minimized over the long term. The guidelines should put greater emphasis on the treatment of moderate- and low-risk patients, since preventing the development of atheromatous plaques is far simpler than preventing their return.

3. The Importance of Nonpharmacological Treatment

The guidelines place a great amount of emphasis on the effects of lifestyle changes such as diet, physical activity, and other habits of healthy living on the different plasma lipids associated with the atherosclerotic process. The recommendations related to lifestyle modifications aimed at reducing general cardiovascular risk, and dyslipidemias in particular, are presented in great detail, including which foods are more or less advisable according to their beneficial or deleterious effects on cardiovascular risk, physical activity, and smoking cessation, which is essential in all cases.

In addition, and for the first time in guidelines of this sort, some thought is given to the results and possible indications for the controversial nutraceuticals. Of the many functional foods and diet supplements that are promoted as being beneficial for people with dyslipidemia and in the reduction of cardiovascular risk, the guidelines only recommend foods enriched with phytosterols (1-2 g/day) for people with elevated total cholesterol and LDLc levels in which the total cardiovascular risk level does not justify the use of statins.

Although these recommendations are clear and indisputable, it is interesting that no specific mention is made of the Mediterranean diet, nor do we find an explicit recommendation for the length of attempts to treat solely with lifestyle changes before starting pharmacological treatment, in contrast to the 3 months recommended by the ATP III.[3]

4. Choice of Lipid-lowering Drugs: Emphasis on Statins

The discussion of the pharmacological properties and practical aspects of use for all available lipid-lowering drugs is well-developed and appropriate. The emphasis on statins as the essential treatment for cardiovascular prevention is logical, given the large number of studies that have demonstrated their efficacy in prevention.[2] The guidelines recommend wide prescription of statins, even the highest allowable or tolerable doses, in order to reach the previously mentioned LDLc goals. For patients with statin intolerance, the recommendation is for bile acid chelating agents or niacin, although this was published before the AIM-HIGH[19] study was prematurely terminated due to lack of effectiveness of this treatment[20] (the HPS2-THRIVE study, however, is ongoing). Absorption inhibitors are not recommended with much zeal, although they are mentioned in possible association with low doses of statins in patients whose poor tolerance impedes prescribing adequate statin levels, or with bile acid chelating agents or niacin (a combination virtually unexplored in our country). It is also logical that the guidelines assign only a marginal role to fibrates, since new studies point towards issues in their safety, which is questionable at the least, as well as the absence of any effect on mortality and long-term cardiovascular complications. It is interesting to point out that the guidelines extensively discuss combinations of drug treatments, establishing indications for combined lipid-lowering drug treatment and its adverse reactions. Niacin (nicotinic acid) is the drug of choice for treating low LDLc levels.

With regard to safety, the primary document mentions that the majority of statins, with the exception of pravastatin, rosuvastatin, and pitavastatin, are significantly metabolized by cytochrome P450, which could provide an advantage in terms of safety. Additionally, statins should be used in patients with renal failure, since these compounds are preferentially eliminated through the hepatic pathway (fluvostatin, atorvastatin, and pitavastatin). Recently, the Food and Drug Administration (FDA) released an alert regarding the increased risk of myopathy and rhabdomyolysis with 80mg doses of simvastatin.[21] Although not implemented in Spain, it is indicated on the technical data sheet for this drug. The guidelines also recommend that doses not exceed 10mg/day of simvastatin in patients taking amiodarone, verapamil, or diltiazem, and not exceed 20mg/day of simvastatin when taken together with amlodipine, all of which are very commonly used drugs in Spain.

Although the guidelines have been very exhaustive and clear on several aspects of the management of patients with dyslipidemia, there is a lack of definition of which specific statins may be preferable in each situation. For example, are all statins capable of reaching a target LDLc<70 mg/dl? The table with supplementary material that shows the % reduction in LDLc necessary to reach target goals derived from baseline values could be completed by including the type of statin and the dosage used. It is possible that the authors of the guidelines are wary about any aspects that may be misinterpreted as "commercial".

5. Treatment of Dyslipidemias in Special Clinical Situations

Another positive aspect of these guidelines, which without a doubt will aid doctors in facing difficult situations, are the recommendations given for specific populations: familial dyslipidemia, children, females, elderly, metabolic syndrome, DM, patients with acute coronary syndrome/coronary revascularization, heart failure, valvulopathies, autoimmune diseases, kidney failure, transplanted patients, patients with peripheral arterial disease, stroke, and those infected with HIV. The majority of these recommendations have level B or C evidence due to the absence of specific randomized studies. It is interesting to point out that for cases of heart failure, the guidelines do not recommend the use of statins, stating level A evidence (based on several randomized studies that have failed to show effective prevention), with a similar situation in patients with valvulopathies, but in this case level B evidence. As in most other guidelines, this one makes practical considerations on how to monitor patients with dyslipidemias and the most convenient periodicity with which to measure lipids and the treatments applied. The recommendations are simple and plausible, although they are based not on evidence but rather on expert consensus.

DEFICIENT ASPECTS OF THE GUIDELINES

Other lipid parameters

The lipid parameters that are considered as secondary objectives are given little emphasis in the new guidelines. For example, the advantages of using ApoB levels as opposed to LDLc are briefly discussed, and the recommendations on this subject tend to be overly conservative. Yet, the guidelines do attempt to be of practical use in all European countries, despite their differences in social health infrastructure and resources. In any case, they do mention that clinical doctors accustomed to using ApoB concentrations can continue to do so, with targets of <80 mg/dl and <100 mg/dl for patients with very high or high cardiovascular risk, respectively. As regards the parameter of non-HDL cholesterol, the targets set forth do

not differ from those mentioned in the NCEP-ATP III guidelines (<30 mg/dl above the corresponding value for LDLc). Curiously, given the lack of validated targets for HDLc and triglycerides, the guidelines limit themselves to simply pointing this out and do not attempt to set out treatment objectives, not even based on consensus opinions. Lipoprotein(a) is mentioned as a new lipid parameter that can be analyzed in patients with premature vasculopathy, but the guidelines only allude to their treatment, perhaps because of the scarcity of options (it does appear that niacin reduces the levels of this lipoprotein, but with little supporting evidence). It appears clear that statins as a whole have an effect in reducing LDLc, but this effect may not be equivalent in other plasma lipid values, nor the robustness of the data supporting their preventive benefits.

Treatment Algorithms

We always expect guidelines to provide practical treatment algorithms. Perhaps these are not necessary with regard to reducing LDLc levels, and it is quite possible that commercial interference impedes giving more concrete recommendations on which statins and at what dose to prescribe, based on patient values, certain clinical circumstances, or concrete risk levels.

Analysis of Economic Profitability

These guidelines make few references to cost-effectiveness studies. They only suggest caution in prescribing statins, above all in primary prevention for low-risk patients.

CONCLUSIONS AND IMPLICATIONS

The new "Guidelines for the management of dyslipidemias" recently published by the ESC/EAS have come to fulfill the expectations of many health care professionals for updated protocols to inform the management of dyslipidemias. These guidelines lend deserved importance to the following topics: evaluating total cardiovascular risk (SCORE scale), LDLc-reducing treatments with targets that become stricter as individual risk increases, nonpharmacological courses of action, the pre-eminence of statins as basic lipid-lowering drugs, and the treatment of dyslipidemias in patients with various special risk situations. Surely, this approach will appease many groups of health care workers as being more "concrete" or "strict" with regard to margins and limits of treatment, as well as more precise indications, but it is also probable that this document was not written with an emphasis on future studies or publications derived from the guidelines, but rather applicability in daily clinical practice. Although the conservative and realistic outlook is effective, it does not sit well with certain groups of clinical researchers. In this regard, we must point out the large amount of level C evidence (expert opinion, registries, and small studies) in all levels of indications, which is a constant issue in the development of guidelines and consensus documents, and detracts from their rigidity and dogmatism.

Having a complete and updated guidelines document available such as this one requires major efforts in dissemination, adaptation, and use by integrated dyslipidemia health care programs, in which the present guidelines should become an essential tool for health care professionals. We expect that these recommendations will have a positive impact on the quality and efficiency of health care provided to these patients, and promote excellence in clinical practice. This is only feasible with the aid of political authorities and scientific communities that must facilitate the implementation of these guidelines. One aspect that must be kept in mind is the economic repercussions of the strict adherence to the recommendations made, which are possibly debatable in moderate and low-risk patients, and can be in direct opposition to the current protocols for economic savings used by health administrators. Cost-benefit analyses based on the prevalence of risk factors in the Spanish population would facilitate an evaluation of the institutional backing that each recommendation should receive.

CONFLICTS OF INTEREST

V.B.: consultant (Astra Zeneca, Pfizer, Recordati) and presentations (Astra Zeneca, MSD, Pfizer, Recordati). E.L.: consultant and presentations (MSD, Astra Zeneca). A.F.O.: consultant (Lilly, MSD, Chiesi, Ferrer) and presentations (Sanofi Aventis, Bayer, Chiesi, GSK, Astra Zeneca, Abbot, Ferrer, Roche, Daichi Sankio, Lilly). M.H.: consultant and presentations (Menarini, Lilly, Astra Zeneca). F.W.: consultant (Rovi). G.B.: consultant (Astra Zeneca, Recordati, Esteve). F.C.: grants (MSD) and presentations (MSD, Astra Zeneca, Ferrer). E.G.: consultants and grants (Astra Zeneca). D.P.: consultant and presentations (Pfizer). G.S.: patents and royalties (Polypill, CNIC).

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