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Controversial issues of the (AHA/ACC) Cholesterol Guidelines: the use and abuse of evidence-based medicine

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ABSTRACT

The 2013 American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol Guidelines reignited interest in cardiovascular prevention. However, despite the strong "evidence-based approach" of the AHA/ACC cholesterol guidelines, the document adds more confusion and controversy than certainties to the field. Critical questions were built without considering the amount and quality of the existing evidence. Instead of highlighting the areas of opportunity to create new knowledge, the document modified previous recommendations with others based on expert opinions. A new prognostic tool was included and a prominent role was given to their results. The tool has major limitations and its use is limited to Caucasians or African Americans aged 40 to 75 years, leaving a large proportion of the recommendations not useful for a significant proportion of the population living outside the USA. The impact of this strategy on the prevention of major cardiovascular events in Europeans does not support the superiority of the AHA/ACC cholesterol document over other guidelines, despite a

RESUMEN

Las recomendaciones del año 2013 de la *American Heart Association/American College of Cardiology* (AHA/ACC) para el tratamiento de la hipercolesterolemia reavivaron el interés por la prevención cardiovascular. Sin embargo, a pesar de su «enfoque basado en evidencias», el documento añadió más confusión y controversia que certezas. Las preguntas fueron construidas sin tener en cuenta la cantidad y la calidad de la evidencia existente. En lugar de poner de relieve las áreas en que se requieren evidencias, el documento modifica las recomendaciones con otras basadas en opiniones de expertos. Fue incluida una nueva herramienta de pronóstico y se otorgó un papel crítico a sus resultados. La herramienta tiene limitaciones mayores; su uso se limita a los caucásicos o los afroamericanos de entre 40 y 75 años, limitando su aplicabilidad en poblaciones que viven fuera de EE.UU. En europeos, el impacto de esta estrategia en la prevención de eventos cardiovasculares no es superior al obtenido con otras guías, pese a que un mayor número de sujetos se califica para el tratamiento con estatinas. En conclusión, la guía de la AHA/

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greater number of subjects qualifying for statin therapy. In conclusion, the AHA/ACC cholesterol guidelines has major limitations that preclude its use in Latin American populations. We must generate the evidence first, and then new efforts to improve the policies could be attempted. (REV MEX ENDOCRINOL METAB NUTR. 2015;2:150-6)

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ACC tiene grandes deficiencias que impiden su uso en poblaciones latinoamericanas. Debemos generar la evidencia requerida, antes de considerar nuevos esfuerzos para mejorar las políticas vigentes.

Palabras clave: Colesterol. Guias clinicas. Medicina basada en evidencia.

INTRODUCTION

The Adult Treatment Panel (ATP) of the National Cholesterol Education Program report of the National Institutes of Health in the USA was a major determinant on the development of strategies for the prevention of cardiovascular disease[1]. Each one of the three previous versions reshaped the focus of national programs and resulted in changes in daily clinical practice[2-4]. The initial report recognized hypercholesterolemia as the major cardiovascular risk factor[2]. The second version integrated a multifactorial view of atherosclerosis, and therapeutic targets were proposed according to the risk level[3]. The third[4] and final version (with its 2008 update[5]) identified groups of patients who have an equivalent risk to patients with coronary heart disease to have a major cardiovascular event and proposed stricter treatment targets for them. The document was criticized due to inaccuracies in the recommendations for the primary prevention group and because a large percentage of its recommendations were based on consensus opinions[6]. In parallel, many organizations created alternative recommendations. Among these are the European recommendations, recently endorsed by the International Society of Atherosclerosis[7]. Nevertheless, ATP-III remained the most frequently cited guideline. The three versions of the ATP were coordinated by a relatively small group of researchers with clinical training (in endocrinology and cardiology) and epidemiologists coordinated by Prof. Scott M Grundy.

The 2013 American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol Guidelines[8] was prepared to take the place of the fourth version of the ATP guidelines. However, it has major differences in design and methodology from the ATP documents. The National Institutes of Health concluded their role as sponsors, a place that was occupied by the American Heart Association and American College of Cardiology. The composition of the committees was renewed. The lead was taken by some members of Dr. Grundy's group (with Niels J. Stone at the head). The panel was composed mainly of members of the sponsoring societies who participated also in the preparation of other clinical guidelines. The document was incorporated into a package of recommendations aimed at treating obesity and cardiovascular prevention. "Evidence-Based Medicine" was the methodology selected for construction documents. Therefore, the document cannot be considered as the fourth version of ATP. It is a new proposal with a different approach.

The report is a document of 397 pages. Each recommendation was built with the best available evidence. Every proposal is qualified by the strength of the evidence that supports it. The randomized controlled clinical studies were considered as the most reliable source of information. The process started with the identification of the critical questions (CQ) to be answered for clinical practice. Questions were constructed using the PICOTSS format (Population, Intervention and exposure, Comparison group, Outcome, Time, Setting, and Study design). A staff, hired by a contractor, searched for and selected the evidence that could be used for supporting the

Table 1. High-risk groups according to the 2013 American Heart Association/American College of Cardiology cholesterol guidelines

Definition	Recommended therapy
Atherosclerotic cardiovascular disease	High-intensity statin therapy
Diabetes mellitus and LDL cholesterol 70-189 mg/dl	
– risk < 7.5%	Moderate-intensity statin therapy
– risk ≥ 7.5%	High-intensity statin therapy
Primary prevention, no diabetes, age 40-75 years and LDL cholesterol 70-189 mg/dl	
– risk ≥ 7.5%	Moderate- or high-intensity statin therapy
LDL cholesterol ≥ 190 mg/dl	High-intensity statin therapy

LDL: low-density lipoprotein.

recommendations. They applied the criteria set by the Panels and Work Groups, in which a heterogeneous set of participants were involved. Independent experts verified the quality of the evidence and made the corresponding qualifications.

MAIN PROPOSALS OF THE DOCUMENT

The identification of four groups with the greatest risk of a cardiovascular event

The groups are shown in table 1. There are major differences in the definitions applied here for the "high risk group" compared to that proposed in the ATP-III and European guidelines.

The use of a new tool to estimate cardiovascular risk and the reclassification of 10-year risk strata (< 5, 5-7.5, and > 7.5%)

The new tool provides estimates for having a major atherosclerotic cardiovascular event in a 10-year period and for the expected lifetime. It can be used in Caucasians or Blacks within the age range of 40-75 years. This tool combines the Framingham Study sample with three additional major studies: ARIC (Atherosclerosis Risk in Communities), the Cardiovascular Health Study and CARDIA (Coronary Artery Risk Development in Young Adults). As a result, longitudinal information of 11,240 Caucasian women (902 cardiovascular events), 9,098 Caucasian men (1,259 cardiovascular events), 2,641 Black women (290 cardiovascular events), and 1,647 Black men (238 cardiovascular events) were added[9]. The tool includes coronary outcomes and stroke. However, ethnicity and gender have major effects on the results. Assuming the same parameters of blood lipids, blood pressure, and age, the estimated value can vary from 2.1% for Caucasian women, to 3.0% for African American women, 5.3% for Caucasian men, and 6.1% for African American men. The C value of the tool, an estimate of the precision of the prediction, ranged from 0.713 (in Black men) to 0.818 (in Black women). Calibration of the tool (assessed using the chi square test) has a minimum value of 4.86 (in Caucasian men) and a maximum of 7.25 (in Black women). The authors acknowledged that the tool overestimates the risk in low-risk cases. Also, they recognized that it is not possible to ensure accuracy in other age groups or other ethnic groups.

The selection of the strata was based on the risk/benefit ratio observed in the statin trials. The 5% threshold is the point where the benefits outweigh the risks in most cases. However, this categorization is applied in the document as synonymous for being in a low-risk group. The Authors decided by consensus to move up the cutoff point to 7.5% for identifying high-risk cases and for considering the use of high-dose statin therapy, due to the overestimation of the risk by the tool in low-risk groups. Moderate-intensity statin therapy was recommended for individuals with a 10-year risk between 5.0-7.5%.

The prescription of statin therapy and its intensity is based on the individual's risk rather than their low-density lipoprotein cholesterol

Statin therapy was stratified in two intensity levels. Moderate intensity assumes a 35% relative risk reduction, a 30% LDL cholesterol change, one excess case of incident diabetes per 100 individuals under treatment, and the number of cases needed to prevent one major cardiovascular event ranges between 40 and 55. It is achieved by using atorvastatin 10-20 mg/day, rosuvastatin 5-10 mg/day, simvastatin 20-40 mg/day, or the equivalent dosage of the other statins. High intensity assumes a 50% relative risk reduction, a 50% LDL cholesterol change, three excess cases of incident diabetes per 100 individuals under treatment, and the number of cases needed to prevent one major cardiovascular event is close to 30. It is achieved by using atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day. The LDL cholesterol measurement is required only to verify that expected changes in LDL cholesterol happened. The targets proposed in the ATP-III (< 130 mg/dl in primary prevention or < 100 or 70 mg/dl in secondary prevention) were eliminated because the authors did not include any paper that could be considered as evidence to support their existence.

The rejection of the use of other drugs besides the statins for cardiovascular prevention through modification of blood lipids

This recommendation was based on the negative results reported with the use of fibrates or niacin in randomized clinical trials. The Authors did not consider the potential limitations of these reports. *Post hoc* analyses of the same trials reached contradictory conclusions[10]. The implications of this recommendation in daily practice are remarkable. It would not be necessary to adjust the lipid-lowering therapy based on LDL cholesterol concentrations after using the highest statin dose corresponding to the intensity level selected based on the cardiovascular risk, or to combine with other lipid-lowering drugs in cases where treatment goals besides LDL cholesterol are not achieved[11].

Before accepting the recommendations of clinical guidelines, health professionals should know the clinical profile of the individuals that qualify for treatment under its use. The information is available to evaluate the AHA/ACC cholesterol guidelines. Pencina, et al.[12] described that the application of the AHA/ACC cholesterol guidelines increases the number of subjects that qualify for statin therapy in the USA. The growth is remarkable; its application moves the percentage of statin users in the 40-75 years US adults group from 37.5% (using the ATP-III guidelines) to 48.6%, resulting in 8.2 million additional patients. The increment is limited to two of the four risk categories (patients having a 10-year risk ≥ 7.5% or with diabetes). Due to the weaknesses of the prediction tool, as described above, a large proportion of subjects over 60 years of age, free of cardiovascular disease, have a predicted risk high enough to qualify for high-intensity statin therapy despite having cholesterol concentrations < 200 mg/dl. This is more common in African Americans due to the inclusion of stroke among the outcomes considered in the prediction tool. On the other hand, young individuals with primary or secondary etiologies of dyslipidemia will not be considered as having a cardiovascular risk high enough to qualify for statin therapy, despite the well-known atherogenicity of several of these conditions (e.g. familial combined hyperlipidemia or rheumatoid arthritis)[13,14]. Also, patients younger than age 53 will need the coexistence of more than two risk factors to be candidates for statin therapy if their cholesterol concentration is < 300 mg/dl. On the other hand, despite that the number of patients with diabetes candidates for statins increased under the AHA/ACC cholesterol guidelines, some controversial issues are present[15]. This document recommends moderate-intensity statin therapy for the majority of patients with diabetes younger than age 53, even in the presence of LDL cholesterol concentrations between 160-189 mg/dl. Since moderate-intensity statin therapy results in a 30% decrease of LDL cholesterol, a large proportion of these patients will have LDL cholesterol concentrations > 100 mg/dl, the target considered as the major lipid goal for cardiovascular prevention in

diabetes[16]. In addition, a large proportion of the patients with diabetes older than age 53 will qualify for high-intensity statin therapy, despite having cholesterol values < 200 mg/dl. In summary, the clinical profile of the primary prevention group that is considered for having statin therapy is not even similar to the inclusion criteria of the trials that the guidelines were built upon. Meanwhile, young patients with diabetes may be undertreated, and others because of their age will be exposed to extremely low cholesterol concentrations.

Furthermore, the ultimate parameter to evaluate a guideline is the ability to improve health outcomes. Kavousi, et al.[17] compared the potential consequences of the application of several guidelines (including the AHA/ACC cholesterol document) for the prevention of cardiovascular disease in a European cohort composed of adults older than age 55. The biggest number of cases under statin therapy was observed with the use of the AHA/ACC cholesterol guideline. Despite that, the predictive power of this approach was not different from that found for the ATP-III guideline (AUC: for AHA/ACC 0.67 and for ATP-III 0.68). In addition, both US documents were below the predictive power of the European recommendations (AUC: 0.76). All three models had a poor calibration and moderate discrimination. This evidence clearly shows that cardiovascular prevention is a work in progress. The current risk tools are imprecise; the information that the scales provide could not substitute the clinical judgment.

Although the merits of "evidence-based medicine" are beyond dispute, the achievement of its objectives depends on the proper construction of the questions, the existence of the evidence, its quality, and its proper interpretation. The authors of the document took special care in building clinical questions. However, they made questionable decisions in scoring and interpretation of evidence. The rating system, to advantage the controlled clinical trials, determined that the pharmaceutical industry and some few international consortia are the main source of high-quality evidence. Critical questions were built without considering the amount and quality of the existing evidence. Instead of highlighting the areas of opportunity to create new knowledge, the document modified previous recommendations with others based on expert opinions. An example is the removal of the LDL cholesterol goals. The authors mention that no dose-titration statin study has shown that further reduction in cardiovascular mortality results from the achievement of a specific LDL cholesterol target. This statement is tricky and based on a wrong conceptual background. It is tricky because they ignore the GREACE study (Greek Atorvastatin and Coronary Heart Disease Evaluation)[18], in which 1,600 coronary heart disease patients were randomized to receive usual care (in which the LDL cholesterol goal was set by the clinical judgment of the treating physician) or structured care (in which the atorvastatin dose was titrated to achieve LDL cholesterol < 100 mg/dl) for a three-year period. Despite the relatively small sample size, the GREACE study showed a remarkably significant decrease in every cardiovascular outcome (e.g. cardiovascular mortality of –47% and stroke –47%). In addition, as stated by Sniderman, et al.[19], the AHA/ACC cholesterol guideline is based "in the risk-benefit paradigm, that states that the relative benefit of LDL lowering is constant, irrespective of the baseline level of LDL. Thus, LDL-C lowering at a low baseline LDL-C should produce substantial clinical benefit and whenever absolute cardiovascular risk is high, benefit from statin therapy should also be substantial". The Cholesterol Treatment Trialist meta-analysis, including 26 studies and the information of nearly 150,000 patients, show that there is a direct relation between LDL cholesterol lowering and the absolute benefit of the intervention[20]. Thus, it cannot be assumed that everybody, regardless of the basal cholesterol concentration, will have a similar absolute risk reduction derived from the same statin dosage. The new recommendation will result in extreme reductions in LDL cholesterol (an intervention whose long-term safety is unknown) or accepting LDL cholesterol levels during treatment which themselves have been considered as indications for treatment (e.g. LDL cholesterol of 160 mg/dl in patients with familial hypercholesterolemia whose baseline was 320 mg/dl). Boekholdt, et al.[21] provide evidence that the second scenario has occurred during the statin trials and it may contribute to the residual risk that

persists in the groups in which the statin-based intervention is implemented. They reported large interindividual variability in the reduction of LDL cholesterol in a meta-analysis of several of the major statin trials (including 38,153 patients). More than 40% of trial participants assigned to high-dose statin therapy did not reach LDL cholesterol < 70 mg/dl. In addition, they reported that the on-treatment LDL cholesterol has a direct relationship with the absolute risk for having cardiovascular events. Taking as a reference the cases that had LDL cholesterol > 175 mg/dl, the achievement of LDL cholesterol < 100, 75, or 50 mg/dl was associated with an adjusted hazard ratio of 0.56, 0.51, and 0.44, respectively. In summary, the lack of evidence cannot be used as a reason to discard *a priori* previous guidelines or to proclaim superiority of a different approach without having the controlled studies to prove it.

Moreover, the rating of the quality of evidence by the authors is difficult to accept. Studies with serious methodological problems such as ACCORD or AIMHigh, in which the effectiveness of fibrates and niacin was assessed respectively in study samples with a high percentage of patients with normal levels of triglycerides, were taken as evidence to rule out the use of other lipid-lowering drugs[22,23]. In addition, evidence derived from ezetimibe studies was not taken into consideration. The positive results of the IMPROVE-IT study, in which the addition of ezetimibe to simvastatin 40 mg was associated with a lower risk (0.936; 95% CI: 0.887-0.988) for having the primary endpoint, will imply a reconsideration of the evidence included in future updates of the AHA/ACC cholesterol guidelines.

The implications of the use of the AHA/ACC cholesterol guidelines are not minor. Individuals currently receiving lipid-lowering therapy would cease to be covered by health systems because the new tool does not identify them as candidates for statin treatment (as would occur in individuals younger than 40 years with primary hyperlipidemia). In addition, the elimination of the LDL cholesterol goals results in changes in the assessment of the quality of the provision of medical services. The Centers for Medicare and Medicaid Services issued an update to the responsible care organizations in which the LDL cholesterol goals were eliminated, without adding other measures of the efficacy of the lipid-based cardiovascular prevention programs[24]. Finally, the Mayo Clinic released an internet tool (statin choice) designed to help primary care physicians to apply the AHA/ACC cholesterol guidelines and to decide together with their patients if statin therapy should be prescribed based on their potential benefits and risks. The application of this tool does not take into consideration the etiology of the dyslipidemia and the time of exposure to the several cardiovascular risk factors. As a result, there is no specific strategy for patients with primary or secondary hyperlipidemias that are associated with increased cardiovascular mortality, such as those associated immunosuppressors, antiretrovirals, inflammatory diseases, renal failure, or nephrotic syndrome. Other guidelines, such as the European or Canadian positions, identify these groups as high-risk and candidates for drug treatment regardless of the estimated risk prognostic tool.

The publication of a clinical guideline generates enthusiasm and interest. Despite the strong "evidence-based approach" of the AHA/ACC cholesterol guidelines, the document adds more confusion and controversy than certainties to the field. Critical questions were built without considering the existing evidence. As a result, some of the main recommendations are based on expert opinions. Furthermore, a new prognostic tool was included and the results are critical for the end result of the whole guideline. Besides the above-described limitations of the tool, its use should be limited to Caucasians or African Americans aged 40 to 75 years, leaving the document not useful for a large proportion of our population. Finally, the measurement of the impact of the strategy on the incidence of outcome to be avoided does not support the superiority of the AHA/ACC cholesterol document over other guidelines.

In conclusion, this position document should not distract our attention. There are many areas in the cardiovascular arena that require further study. We must generate the evidence first, and then new efforts to improve the policies could be attempted.

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