A Latin American Perspective on the New ACC/AHA Clinical Guidelines for Managing Atherosclerotic Cardiovascular Disease

Ada Cuevas · Antonio Arteaga · Attilio Rigotti

Abstract Atherosclerotic heart disease and stroke are leading causes of disability and death worldwide, affecting not only developed countries, but also low- and middle-income regions. Different strategies for handling dyslipidemia as a critical pathogenic risk factor for atherosclerosis have been proposed. However, these recommendations are not applied at all in many countries or even in whole regions of the world. Recently, new US guidelines on risk assessment, lifestyle changes, and high blood cholesterol level treatment to manage atherosclerotic disease were released. In this article, we analyze these new guidelines and discuss their potential applications in preventive cardiovascular medicine in Latin America.

Keywords Clinical guidelines · Risk assessment · Lifestyle · Cholesterol treatment · Cardiovascular disease · Latin America · Cardiovascular risk

Introduction

Atherosclerotic cardiovascular diseases (CVD) are the leading causes of disability and death worldwide. Owing to the ongoing epidemiological transition, these diseases will progressively affect not only developed countries, but also an increasing number of people from low- and middle-income regions. Thus, appropriate and wide-reaching evidence-based clinical guidelines are required to effectively prevent and control atherosclerosis.

However, lifestyle and cardiovascular risk and their impact on atherosclerotic disease differ among countries and cultures. Moreover, specific ethnic groups have been underrepresented in cardiovascular risk estimation cohorts and in randomized clinical trials. Thus, appropriate risk assessment and tailored therapeutic approaches are needed to guide proper use of screening, lifestyle recommendations, and drug therapy in different regions beyond developed countries.

Clinical guidelines addressing evaluation and management of cardiovascular risk are complex, and there are often inconsistencies between them. Moreover, they may not be available in many countries/regions of the world. In this article, we examine recent clinical guidelines issued by the American College of Cardiology (ACC) and the American Heart Association (AHA) to manage CVD and their potential implications for medical practice and patient care in Latin America.

Overview of Cardiovascular Risk in Latin America

According to the World Health Organization, about one quarter of deaths occurring annually in Latin America are due to CVD [1]. Information on cardiovascular risk factors in Latin America comes predominantly from nonrepresentative cross-sectional studies that are mostly based on self-report or studies with small and biased population samples. Considering these limitations, major cardiovascular risk factors, including obesity, hypertension, hypercholesterolemia, diabetes mellitus, and tobacco use, are highly prevalent in Latin America and contribute to three quarters of cardiovascular events [2, 3••]. Indeed, traditional risk factors account for almost 90 % of the

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population-attributable risk for a first myocardial infarction in Latin America [4].

However, even though dyslipidemia is very prevalent, its prevalence differs among different Latin American countries [5], and the most frequent lipid alteration detected in selected samples and national surveys is a low level of HDL cholesterol associated with high levels of triglycerides rather than a high level of LDL cholesterol [5–7]. Also, the prevalence of smoking is among the world's highest in Chile and Argentina, but not in other countries of the region [2]. In addition, the female population in Latin America has a lower rate of mortality from coronary heart disease and a higher rate of mortality from cerebrovascular disease than North American women [8]. Furthermore, Latin American populations exhibit a high prevalence of abdominal obesity and metabolic syndrome, similar to or even higher than that in high-income countries [9–11]. This epidemiological situation is attributed to lifestyle changes, migration from rural to urban areas, and higher abdominal obesity in Latin American populations compared with other ethnically different populations [11]. These findings not only forecast an increased rate of CVD for the coming decades within this region, but also underscore a different cardiovascular risk profile compared with that in developed countries.

As mentioned, we should keep in mind that Latin America is a heterogeneous region featuring significant genetic and environmental variability among different countries. Some areas, such as Chile, Argentina, and southern Brazil, exhibit a substantial Caucasian background, with consumption of a more Western-type diet, whereas Central America displays a predominantly Amerindian ancestry, with high intake of grains and vegetables. Therefore, cardiovascular risk assessment and CVD expression in one country may significantly diverge from those in another country.

On the other hand, earlier studies in Latin American and Hispanic populations showed relative lower cardiovascular and all-cause mortality despite a high prevalence of traditional risk factors and reduced socioeconomic status and barriers to health care, leading to the "Hispanic paradox" concept. Even though this proposal has been disputed because of problems in population sampling, confounding bias, and data reliability [12], a recent systematic review and meta-analysis supports this concept [13•]. Additional studies are required to identify the mechanisms mediating this apparent protective status against CVD in Hispanics.

Thus, it is important to establish evidence-based criteria for evaluation of cardiovascular risk in Latin America as well as for the implementation of preventive and therapeutic strategies against CVD in these populations.

Recent Guidelines on Cardiovascular Risk Evaluation and CVD Prevention

Among the clinical recommendations issued by different organizations, National Cholesterol Education Program (NCEP) reports on detection, evaluation, and treatment of high blood cholesterol levels in adults represented a significant contribution widely used in clinical practice [14, 15]. These guidelines improved medical care by more effectively defining and targeting blood lipid parameters, in particular LDL cholesterol, as key drivers in the initiation and progression of atherosclerotic CVD.

While a new NCEP report was delayed, other organizations from North America, Europe, and Asia and the International Atherosclerosis Society (IAS) updated their strategies for the management of dyslipidemia. These guidelines were based on different types of new scientific support, including epidemiological and genetic studies as well as clinical trials, but most of them built upon previous recommendations.

Recently, the ACC and the AHA, in collaboration with the National Heart, Lung, and Blood Institute and other medical governing bodies, released long-awaited U.S. guidelines on risk assessment [16••], lifestyle modification [17••] and high blood cholesterol treatment [18••] to manage atherosclerotic cardiovascular disease. This update represents the first major US guideline revision since 2001–2004 and is aimed at replacing previous NCEP guidelines. The guidelines are significantly different from former approaches, including a broader calculation of cardiovascular (nonfatal myocardial infarction, coronary heart disease death, nonfatal and fatal stroke) risk and its wider applicability in women and African American populations [16••]. Moreover, new recommendations for cholesterol-lowering therapy are essentially based on clinical trial evidence derived from systematic reviews and meta-analyses, favoring the choice between fixed moderate or high statin dosing—rather than pursuing LDL cholesterol goals—according to the estimated cardiovascular risk [18••].

In contrast, evidence-based guidelines on lipid management and cardiovascular risk reduction from low- and middle-income countries are extremely scarce. Indeed, a recent survey in Africa indicated that CVD and hypertension guidelines are available in only two thirds of the countries and cholesterol guidelines are lacking in 90 % of this region [19]. Furthermore, many aspects of these CVD guidelines are significantly behind current standards. To our knowledge, a similar comprehensive review of cardiovascular risk evaluation and management guidelines has not been conducted in Latin America. On the basis of current recommendations and recent clinical trials, a Latin American perspective on clinical lipidology was published [20], but it did not embody a standard clinical guideline and was not based on evidence from actual studies performed within the region.

The proposal of the IAS on management of dyslipidemia represented an important effort to include a worldwide view and international consensus on the subject [21••]. This guideline suggests making adjustments (e.g., cardiovascular risk assessment calibration, metabolic syndrome definition) as needed for particular countries/populations. Remarkably, these modifications are very limited and with little support for Latin American nations. Adequate risk assessments as well as population-built and individually guided interventions derived from evidence-based medicine are urgently required to successfully prevent CVD in Latin America.

The 2013 ACC/AHA Guideline on Cardiovascular Risk Assessment

Risk assessment to accurately identify individuals who will largely benefit from lifestyle and pharmacological interventions is essential to manage atherosclerotic CVD in routine clinical practice.

The Framingham risk score (FRS) has been one of the most used models for calculating cardiovascular risk. Owing to inherent population bias (an exclusively white sample) and limited scope of the outcome (coronary heart disease alone) in the original cohort, the FRS overestimates cardiovascular risk in some populations and underestimates it in others, which has led to recalibration before its use in some non-US populations.

The new ACC/AHA guideline provides a risk calculator for a broader atherosclerotic disease outcome that is more relevant to additional segments of the US population, including women and African Americans, which were not appropriately assessed by the standard Framingham tool [16••]. This new approach allows risk assessment based on data that primary care health professionals could easily collect and it can be straightforwardly implemented in routine clinical practice. Even though the new risk equations can be more representatively applied to US inhabitants, their accuracy has already been criticized, and limitations were indeed explicitly acknowledged in the new guideline. On the basis of data from several external validation cohorts [22•], the proposed algorithm overestimates the actual observed risk, leading potentially to overprescription of statins in primary prevention. Thus, it needs to be more formally evaluated in randomized controlled trials of screening strategies using clinical events as outcomes. Further guideline updates should increase the accuracy of the risk calculator to improve treatment decisions.

Moreover, selection of adequate thresholds to identify individuals at risk is influenced by ethnicity. Despite improvements due to inclusion of statistics from African Americans, risk evaluation data from other races/ethnic groups (e.g., Hispanic and Asian American) were insufficient, precluding their inclusion in the final analyses of the new guideline [16••]. Thus, the strengths and weaknesses of the risk estimator

beyond white Americans and African Americans are currently unknown.

Some nontraditional risk factors (e.g., high-sensitivity C-reactive protein) were not recommended for routine use in risk stratification because there was not enough evidence supporting their use [16••]. However, they can be applied when clinical judgment suggests that a patient's risk assessment remains ambiguous.

As mentioned, risk factors and patterns for CVD may differ significantly between populations. In contrast to high-income countries, cardiovascular risk estimation based on appropriate and well-designed cohort studies in Latin America is still lacking. Thus, adaptations of guidelines from developed regions will unavoidably happen broadly around the world. A recent review indicated that the amount and the quality of the evidence on testing and validating US or European cardiovascular risk prediction models in Latin American populations and/or Hispanics in the USA is low to moderate at best [23]. When the Framingham-based NCEP risk algorithm was used, the relative distribution of cardiovascular risk in a representative adult Chilean population surveyed in 2003 was similar to that reported in the USA [24]. However, the standard FRS—without prior recalibration—overestimates cardiovascular risk in Latin Americans and Hispanics living in the USA [23]. In Chile, Framingham equations have been adjusted on the basis of lower overall cardiovascular event rates [25], even though a validation study should be performed to assess their actual predictive power.

If the new risk calculator proposed by current ACC/AHA guidelines is not appropriately recalibrated, it is likely that it will miscalculate cardiovascular risk in Latin America. Thus, its application in Latin America should be tested as well as adjusted and revalidated. More significantly, development and verification of locally originated risk prediction rules should be a major task to be implemented within the region. Ongoing cohort studies (INTERHEART [4], CESCAS-I [26], and ELSA [27]) in Latin America will provide opportunities to develop our own cardiovascular risk calculators, which will help clinical decision-making, guide therapy, and measure risk trends at population levels.

The 2013 ACC/AHA Guideline on Lifestyle Management To Reduce Cardiovascular Risk

After individual cardiovascular risk has been defined, the ACC/AHA guidelines provide evidence-based recommendations for lifestyle changes to reduce serum cholesterol levels and blood pressure and the burden of CVD [17••]. This guideline encourages healthy nutrition, promoting overall dietary patterns (low sodium consumption and high consumption of vegetables, fruits, whole grains, low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts)

rather than individual dietary components. Also, regular physical activity, tobacco avoidance, and maintenance of normal body weight are recommended as critical components of lifestyle intervention for CVD prevention.

The specific recommendations for lowering LDL cholesterol levels are consumption of the dietary pattern mentioned above, following plans such as Dietary Approaches to Stop Hypertension, US Department of Agriculture, or AHA diets. Lifestyle changes should be promoted vigorously for those patients who do not achieve the expected decrease in LDL cholesterol levels, along with consideration of adding a non-statin drug to the treatment.

Whereas the ACC/AHA guideline on lifestyle is inclined to using Dietary Approaches to Stop Hypertension, US Department of Agriculture, or AHA food patterns rather than the Mediterranean diet, previous (Lyon Heart Study) and recent (PREDIMED trial) evidence from large randomized clinical trials with event-driven outcomes should be strongly considered to indicate the Mediterranean diet for CVD prevention [28•]. The Mediterranean diet, even when applied in non-Mediterranean populations, can be regarded as one of the most effective approaches for the prevention of CVD.

Application of these recommendations to Latin America may be challenging because of the ongoing epidemiological transition in the region as well as different genetic, economical, social, and cultural characteristics compared with other populations, requiring specific adaptations of lifestyle programs.

In recent years, Latin America has experienced a marked decrease in the consumption of cereals, vegetables, fruits, whole grains, and fiber, whereas intake of animal proteins, fats, sugar, and processed foods has increased [29, 30]. Additionally, physical activity has decreased, mainly in urban areas. These lifestyle changes have been attributed to the socioeconomic development of some regions, leading to a decrease in undernutrition and infectious diseases, but concomitantly a rapid increase in obesity and related comorbidities [30]. Thus, it is crucial to have more and updated information about dietary patterns and nutritional status in different regions of Latin America, because there are large variations in the nutritional transition, according to their economic and social progress. This evidence would allow better and more individualized strategies to deal with the dual nutritional problem of Latin America: undernutrition in some of the poorest areas and obesity and related diseases in more developed regions.

Some studies have suggested that Latin American populations exposed to unhealthy lifestyle patterns appear to develop more metabolic abnormalities than other populations, even in the presence of lower levels of obesity [31]. Moreover, the International Day for Evaluation of Abdominal Adiposity study has shown that abdominal adiposity is very frequent in Latin American women with normal body mass index and is significantly associated with diabetes and CVD [32]. These observations have led some international organizations to suggest lower cutoff levels of waist circumference (similar to those in Asian populations) to define abdominal obesity in Latin America [33]. However, these thresholds remain to be determined.

Moreover, in countries (e.g., Chile) that rapidly adopted food patterns associated with a higher risk of obesity and CVD, it should be beneficial to promote the return to traditional cooking patterns and meals, which in some regions share features of the Mediterranean diet. Furthermore, it is important to investigate, develop, and promote native food products that may have advantageous effects by decreasing the presence of some cardiovascular risk factors. For instance, both *maqui* in Chile and *acai* in the Amazonas contain high levels of antioxidants [34, 35], and may be useful in a balanced diet.

Recent evidence indicates the relevance of incorporating new lifestyle policies and programs based on specific problems in the region. Indeed, the main barriers against consumption of fruit and vegetables in six Latin American countries are the lack of public health and policymaking support, which is crucial to develop an effective advertising campaign to achieve significant results [36]. Early implementation of these policies will be more effective in preventing the obesity epidemic rather than applying them when the problem is more advanced [37].

Another important issue in Latin America is tobacco consumption. Recent data showed that some Latin American countries exhibit a very high prevalence of smoking [2, 38]. Therefore, urgent and aggressive preventive policies should be implemented to address this risk factor in Latin America. Some countries have already established national campaigns and new legislation against tobacco consumption. Follow-up of these population-level measures will allow evaluation of health impact and cost-effectiveness in order to apply them in other less developed countries.

Although they support the use of lifestyle changes in primary prevention, the new ACC/AHA guidelines also promote a more generalized use of statins in populations without CVD but with an estimated 10-year cardiovascular risk of 7.5 %. In contrast, recently published IAS guidelines favor the use of lifestyle intervention in primary prevention to reverse unhealthy habits, which are considered the main underlying cause of atherosclerosis, focusing on the use of statins in people with the highest cardiovascular risk [21••]. This latter approach seems to be more reasonable in some Latin American countries, where other social problems need to be solved within a context of limited economic resources.

The challenge for the coming years is to translate these guidelines into diets and lifestyle patterns that are both appealing and effective in Latin Americans using anthropologically and culturally acceptable ways that will make people change their long-standing habits.

The 2013 ACC/AHA Guideline on Lowering Blood Cholesterol Levels To Reduce Atherosclerotic Cardiovascular Risk

Previous NCEP reports and the updated Canadian and European guidelines have emphasized how to manage dyslipidemia, reaching specific LDL cholesterol goals according to the individual cardiovascular risk. These lipid goals were defined on the basis of epidemiological and genetic studies as well as indirect evidence from randomized clinical trials.

Beyond high-income nations, NCEP guidelines have been applied in some Latin American countries [24, 39, 40]. Using this well-known strategy, a preliminary study based on a representative national health survey showed that 71 % of Chilean adults meet their LDL cholesterol goals. Of those at high and very high risk, only 15 % and 2 %, respectively, had the target LDL cholesterol levels [24]. Even though most adults living in Chile meet the risk-adjusted LDL cholesterol goals, large fractions of the high-risk population—which would most likely benefit from cholesterol-lowering drugs—remain undertreated. However, a cost analysis indicated that using drugs to achieve the LDL cholesterol goals in Chile would represent a major economic burden to the health system [24].

In contrast, the new ACC/AHA guidelines abandon titrating cholesterol-lowering therapy to achieve target LDL cholesterol levels [18••]. The panel made this recommendation because it required randomized clinical trial evidence to support continued use of prespecified LDL cholesterol targets. Instead, the new guidelines primarily advise the choice of moderate- or high-intensity statin therapy in those most likely to benefit for primary or secondary CVD prevention [18••]. Indeed, available clinical trials have demonstrated the utility of fixed statin doses in lowering LDL cholesterol levels by at least 30 % from the baseline against placebo or have compared the efficacy of fixed doses of high-intensity versus moderate-intensity statins regardless of the baseline LDL cholesterol level. Even though follow-up laboratory measurements are not advocated for checking progress towards specific LDL cholesterol levels per se, they are still recommended for assessing medication response and adherence [18••]. Similarly, the recently updated clinical guideline on lipid management in chronic kidney disease does not support a specific on-treatment LDL cholesterol target for statin dose adjustment based on LDL cholesterol levels [41].

The new guideline defines four groups where the benefit from statin therapy outweighs the potential risks: (1) individuals with clinically evident atherosclerotic CVD; (2) individuals with LDL cholesterol levels greater than 190 mg/dl; (3) diabetic individuals who are 40-75 years old; and (4) individuals with a 10-year cardiovascular risk of 7.5 % and who are 40-75 years old [18••]. Although these risk groups are similar to those defined in previous and updated recommendations, they are now more strictly delineated for statin therapy as specifically supported by major clinical trials.

Some of the significant strengths of this new approach are (1) simplification of the decision-making algorithm, (2) emphasis on preventing stroke as well as coronary heart disease, (3) focus on statin-based therapy rather than other lipid-lowering drugs, and (4) recognition that the benefits of statins in very high cardiovascular risk conditions (previous clinical atherosclerosis, LDL cholesterol level above 190 mg/dl, diabetes) offset the potential adverse effects.

This approach represents a significant divergence from current strategies and has already generated some controversy [22•, 42, 43•]. The potential resistance to give up the hypothetical benefit of the treat-to-goal strategy remains to been seen. However, we must keep in mind that previous recommendations using LDL cholesterol targets may lead to undertreatment with a suboptimal dose of statins because a lipid goal has been reached or may lead to overtreatment to achieve a target with non-statin drugs that have not been shown to reduce the risk of events in clinical trials.

A major concern about this new guideline arises from its application in primary prevention, in particular in a large fraction of subjects in which the new cardiovascular risk calculator will be applied [22•, 42, 43•]. Assuming a potential overestimation of risk together with the lower cutoff for predicted 10-year high risk, overprescription of statins may be a major consequence. However, members of the expert panel have disputed predictions that the number of patients taking statins would dramatically increase under the new guidelines. A rough estimation using this risk stratification tool suggests a potential massive statin use ("statinization"), with about one billion people worldwide being prescribed statins for primary prevention [43•]. This situation may be relevant in low- and middle-income countries owing to the rising prevalence of risk factors and aging populations. In addition, critics have objected that the proposed approach to decide on statin treatment is not actually based on available evidence because statin therapy in clinical trials has not been indicated using global risk estimation [22•].

On the other hand, the previous NCEP report endorsed all the major types of available lipid-lowering drugs and identified statins as a first choice for starting pharmacologic therapy, but it recommended the use of other drugs for reaching LDL cholesterol goals. In contrast, in the new cholesterol guidelines, non-statin drugs—used alone or in combination with statins—are not generally recommended because sufficient clinical trial evidence is lacking to support their routine use—in addition to statins—to prevent CVD [18••]. However, trials that support the new recommendation have not assessed the benefit of combined lipid-lowering therapy in statin-treated patients with persistently high LDL cholesterol levels. In addition, tolerability of high-dose statins can be a problem for some patients, and thus combined cholesterol-lowering

therapy may still be an option in order to achieve more than 50 % reduction in LDL cholesterol levels. Indeed, the panel indicates that non-statin pharmacotherapy can be used in patients who do not respond as expected to statins or who experience statin intolerance [18••].

Scaling up coverage of cholesterol-lowering interventions to prevent CVD in high-risk individuals in low- and middle-income countries should have a major impact in reducing chronic disease worldwide. In fact, preventive measures used in North America and Europe have been applied in Latin America. Although statins are increasingly used in high-income countries, there is, however, lower implementation of high cholesterol level screening and treatment in low- and middle-income countries [44]. For instance, less than 5 % of patients with CVD in low-income countries use statins for secondary prevention [45••]. Country-level economic factors influenced rates of drug therapy more than did individual-level factors, such as age, gender, education, smoking habits, and presence of obesity, hypertension and diabetes.

In addition, the cost-effectiveness and feasibility of statin therapy in countries at low to middle levels of economic development require evaluation [46]. However, many statins are available as generic products and at relatively low cost in different regions, which may lead to increasing use in countries with restricted health care resources. We must convince health authorities about the importance and benefits of incorporating use of these drugs in our public health systems for primary and secondary prevention. In this regard, a multidrug approach (a polypill including statins) for prevention of CVD in these countries may help to effectively meet a significant fraction of the global goal of reducing chronic disease death rates by an additional 2 % per year with a moderate increase in health expenditure [47].

Conclusions

The new ACC/AHA guidelines for statin-based management of high cholesterol levels as a risk factor for atherosclerosis are strongly based on evidence from clinical trials. It is expected they will be more regularly updated as evidence gaps are addressed in new clinical end-point-based studies. In addition, it would be very valuable if the proposed approaches (e.g., new risk calculator, risk cutoff levels, risk-based drug therapy decision) are also prospectively evaluated against other risk assessment models (e.g., alternative risk thresholds) and/or alternative interventions (e.g., LDL-cholesterol-target-based drug treatment), including patients from low- and middle-income countries. However, we should not forget that clinical judgment remains critical in risk evaluation, lifestyle recommendations, and drug therapy decision-making.

Owing to the scarcity of regionally based studies, we propose that a group of experts from Latin American countries with support from panel members producing US and non-US guidelines convene to develop a position statement on how new approaches for risk assessment and statin therapy may be adapted and implemented within the region. Moreover, this group may also propose how to take advantage of ongoing cohort studies as well as how to increase participation of Latin American countries in new clinical trials.

In addition, funding new Latin American programs aimed at strengthening research focused on significant regional health problems should have high priority [48]. We must encourage a real partnership among different stakeholders beyond physicians, including allied health personnel, scientific societies, heart foundations, governmental organizations, and patient and general public associations. Taken together, these initiatives will foster both health promotion at the population level and CVD prevention at the individual level in Latin America, using the best available regionally relevant medical evidence from population surveillance to clinical trials.

Compliance with Ethics Guidelines

Conflict of Interest   Ada Cuevas is on the advisory board of MSD, Sanofi-Genzyme, and Amgen.
   Antonio Arteaga declares that he has no conflict of interest.
   Attilio Rigotti is on the advisory board of Merck, and is a consultant for MSD, Pfizer, and Sanofi-Genzyme.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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