

Improving Cardiovascular Risk Stratification in Argentina: an Impossible Task or “Impossible is Nothing”?

Mejorando la estratificación del riesgo cardiovascular en la población argentina: ¿Una tarea imposible o “lo imposible no existe”?

CARLOS G. SANTOS-GALLEGO, JUAN J. BADIMÓN

Cardiovascular disease (CVD) is mainly caused by atherosclerosis complications (1) and is the leading cause of death worldwide. (2) Although new therapies are being developed, (3) 32.3% of mortality in the United States is still due to CVD. (2) The therapeutic strategy “to reduce CVD depends” on the specific cardiovascular risk (CVR) of “each individual patient”. However, the correct CVR stratification and therapy required “at each CVR level” are still controversial.

CURRENT CARDIOVASCULAR RISK STRATIFICATION

In 2001, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) released its actually, the “(NCEP ATP-III)” should appear immediately after “third guidelines” for the identification and treatment of dyslipidemia, (4) which were updated in 2004. (5) These guidelines focused on the identification and quantification of cardiovascular risk factors (CVRF) and significantly increased the number of patients eligible for cholesterol-lowering medication (not only limited to statins). In November 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) issued new guidelines on hypercholesterolemia treatment, (6) which have initiated a major international scientific debate due to the substantial changes introduced regarding European guidelines and previous American guidelines. These guidelines represent a paradigm shift reflected in the following points:

1. Methodology:

- a. While the 2001 guidelines focused on coronary heart disease (cardiovascular death and AMI), the 2013 ACC/AHA guidelines broaden the scope to all CVD, also including stroke and peripheral artery disease (other than coronary heart disease).
- b. The new 2013 ACC/AHA guidelines only consider evidence provided by randomized clinical trials and meta-analyses of these clinical trials, promoting a predominantly statin-centered approach.

However, the NCEP ATP-III 2001 guidelines included systematic review evidences (although not derived from clinical trials), which resulted in considering also other hypocholesterolemic drugs.

- c. Both guidelines have different objectives. The NCEP ATP-III 2001 guidelines were a comprehensive set of recommendations for laboratory assessments, clinical diagnosis, lifestyle changes and pharmacology. However, the 2013 guidelines exclusively focus in answering two questions: i) What is the evidence for the therapeutic goals of LDL-C in both primary and secondary prevention?; ii) what is the efficacy and safety of drugs in the treatment of primary and secondary prevention patients?

2. Cardiovascular risk assessment model

The NCEP ATP-III 2001 guidelines recommended using the Framingham Risk Score (FRS) to assess the risk of developing coronary heart disease (cardiovascular mortality or nonfatal AMI) at 10 years. However, this score did not consider stroke as endpoint and had no racial or geographical variability in the referral samples. The 2013 ACC/AHA guidelines have developed “pooled cohort equations” (PCE) that analyze data from four studies: CARDIA, CHS, ARIC and Framingham. They have also included stroke as an endpoint and have developed specific models for Caucasian and African American subjects, which improves the assessment accuracy by race. Finally, diabetes has been added as CVRF in this model (other than those already included in the FRS, such as age, sex, total cholesterol, HDL-C, systolic blood pressure and smoking).

3. Treatment recommendations

The 2013 AHA/ACC guidelines recommend statin therapy in the following four groups:

- a. Secondary prevention in patients with established atherosclerotic CVD.

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Address for reprints: Juan J. Badimón, PhD - Unidad de Investigación en Aterotrombosis - Cardiovascular Institute - Icahn School of Medicine at Mount Sinai - New York - USA - Tel. 212-241-8484 - Fax: 212-426-6962 - e-mail: juan.badimon@mssm.edu

- b. Primary prevention in patients with LDL-C levels >190 mg/dL.
- c. Primary prevention in diabetic patients with LDL-C between 70 and 189 mg/dL.
- d. Primary prevention in non-diabetic patients with LDL-C between 70 and 189 mg/dL if CVR estimated at 10 years is above 7.5% according to the new PCE calculator. It should be noted that for this fourth group, guidelines recommend a shared decision between the doctor and patient after a thorough discussion considering CVR, statin side effects, lifestyle changes, and of course, patient preferences.

The ACC/AHA 2013 guidelines also suggest that this group of patients with CVR between 5% and 7.5% can also be prescribed statins if there are additional risk factors that favor their reclassification into other higher risk categories: LDL-C >160 mg/dL or family hypercholesterolemia, family history of CVD, ankle-brachial index <0.9, C-reactive protein >2 mg/L or coronary calcium score (either the Agatston index >300 or calcium score above the 75th percentile for age, gender and race). However, in this group with CVR between 5% and 7.5% statin therapy is a potential suggestion, not a recommendation.

Instead of recommending the achievement of specific LDL-C levels, the new guidelines only address the intensity of statin therapy. This is the most controversial aspect of the new guidelines, since the NCEP ATP-III guidelines established LDL-C target levels that had to be met (e.g. <70 mg/dL for secondary prevention). In this regard, the British NICE guidelines use the same criteria that the new American guidelines (they are based on the QRISK2 score that includes stroke, and they do not recommend specific LDL-C levels).

IMPROVING CARDIOVASCULAR RISK STRATIFICATION

These 2013 AHA/ACC guidelines raise a number of questions, upon which the study by Bozzo et al. published in this issue of the Argentine Journal of Cardiology (7) sheds light.

Firstly, there are several CVR scores, which means that none is optimal and that they all have limitations. The original scores often miscalculate the true CVR when widely applied to populations which are different (both genetically, dietary and even culturally) from the population which generated the original score. A classic example is that the FRS (developed in an Anglo-Saxon population with a Western diet) overestimates by almost threefold the true CVR (i.e., it calibrates wrongly) in the Spanish population (with different genetic origin and Mediterranean diet) (8), and had to be specifically calibrated for the Spanish population (REGICOR trial). (9) In fact, a previous study by Masson et al. (10) confirms the poor agreement of the different scores in Argentina: high-risk patients accounted for 6% of the population if the FRS was used, 9% if the EuroSCORE was employed,

2% if the WHO score was applied, and 33% if the 2013 AHA/ACC guidelines were used. There was also poor correlation between the three scores ($\kappa=0.14$), which emphasizes the importance of validating the scores and specifically adapting them to each country. (11). Bozzo et al. (7) confirm these findings, reporting 37% of patients at high risk according to the 2013 AHA/ACC guidelines (CVR >7.5%), very similar to the 33% obtained by Masson et al. (10) Therefore, the study by Bozzo et al. (7) sheds light on the high prevalence of patients at high CVR in the Argentine population and it draws attention to the need of starting strategies for CVR reduction.

A second remarkable factor in this study is PCE "validation" for the Argentine population. The main limitation of the PCE is that they were generated in North American populations, very different from the Argentine population both genetically, dietary or culturally. The study by Bozzo et al (7) is important because it validates these equations in the Argentine population and, although it does not directly measure cardiovascular events, it finds that in the Argentine population the prevalence of carotid plaque (an indirect endpoint of future cardiovascular events) increases with higher CVR strata. This means that PCE are effective to detect carotid plaque, which "validates" their usefulness in the Argentinian population.

This article (7) also provides additional information on a third aspect, on the selection of patients on whom to start treatment with statins. According to Rose's paradox (12), although patients at higher relative risk of suffering cardiovascular events are identified by their high CVR, the highest absolute number of cardiovascular events occurs in patients at low CVR (because, despite their low relative risk, their number in the total population is very high). Therefore, sometimes a population strategy (treating all individuals above a minimum threshold of CVR) is proposed instead of an individualized strategy for each patient. The advantage of this population prevention strategy would be to expand the number of treated individuals, but its disadvantages are treating a large number of individuals who would not need treatment and the increase of side effects from the medication administered.

Nevertheless, this population strategy ignores the heterogeneity of CVD and is the antithesis of personalized or individualized medicine. Cardiovascular risk can be refined by restratifying this population with additional tests or by directly detecting the presence or absence of CVD. The first strategy (additional diagnostic tests) is the one applied by the 2013 AHA/ACC guidelines when they recommend patients with CVR between 5 % and 7.5% for potential statin indication if they meet additional CVR criteria (e.g. LDL-C >160, Agatston >300, C-reactive protein >2 mg/L). A previous study (13) has shown that calcium score is the technique that reclassifies more accurately these subjects at low CVR, with C-reactive protein

and family history of CVD being also useful but at a greater distance. However, the second strategy (direct detection of CVD by carotid ultrasound) is the one applied by Bozzo et al. (7), who demonstrates that it adequately reclassifies patients at intermediate-low CVR. Given that CVD progresses slowly in the early stages, the presence or absence of CVD in a specific patient is the best representation of CVR for that particular patient. In fact, the study of Yeboah et al. (13) shows that the best predictor of CVR is the calcium score, because it is the actual detection of CVD (coronary atherosclerosis) for that patient. A limitation of the PCE is to assign more relevance to age than to other CVRF (age is weighted by a factor of 29.799, twice as much as HDL-C with 13.578 or four times more than smoking with 7.575); therefore, according to these equations an otherwise healthy 70 year-old individual will have almost the same CVR as a younger smoker, with high LDL-C and low HDL-C. Fortunately the study by Bozzo et al. (7) provides a solution: the best estimate of CVR for this subject is obtained through a carotid ultrasound to assessing presence or absence of plaque, which is a far superior estimate of CVR than the estimation provided by the PCE and also much cheaper than the calcium score suggested by Yeboah et al. (13). In addition, the presence of carotid plaque is much more sensitive of CVD than other diagnostic techniques; for example, it was found that up to 34% of individuals with low CVR and calcium score of 0 had carotid plaque, (14) thus allowing their reclassification at higher CVR. Moreover, Bozzo et al (7) show that within each CVR level, the risk of carotid plaque increases when the number of CVRF is larger; therefore, if a carotid ultrasound cannot be performed, the assessment of the absolute number of CVRF offers a restratification of carotid plaque risk without incurring in any CVR overestimation due to age. Thus, in the presence of a patient with CVR between 5% and 7.5% according to the PCE, carotid ultrasound is the best restratification tool for CVR. If carotid ultrasound is not possible, the absolute number of CVRF may help deciding whether to treat with statins or not (if more than 2 CVRF are present, the patient should be treated with statins; otherwise, the CVR is probably due to the overestimation caused by age and statins may not be necessary).

In conclusion, the study by Bozzo et al. (7) confirms the high prevalence of patients at high CVR in Argentina and indirectly validates the 2013 ACC/AHA guidelines for the detection of carotid plaque in the Argentine population. Finally, it shows that the use of carotid ultrasound for the direct diagnosis of CVD is an ideal strategy to assess the population with CVR between 5% and 7.5% and to decide whether to

start statin therapy (using the absolute number of CVRF when this is not available). In conclusion, Bozzo et al. (7) show that it is possible to improve CVR stratification by applying non-invasive imaging tests, i.e. applying personalized medicine.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms in the website/Supplementary material).

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