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Editorial

From Risk Scales to Subclinical Atherosclerosis Quantification Through Non-invasive Imaging: Toward a New Paradigm in Cardiovascular Risk Prediction

De las escalas de riesgo poblacional a la cuantificación de la ateroesclerosis subclínica: hacia un nuevo paradigma en la predicción cardiovascular

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LIMITATIONS OF TRADITIONAL RISK SCALES

Continuous changes to primary prevention guidelines have resulted in better risk factor control, which in turn has significantly contributed to the reduction in rates of atherosclerotic cardiovascular disease (ASCVD). In Spain, approximately half of the decline in coronary mortality has been attributed to a reduction in the major risk factors and the other half to evidence-based treatments.[1] In the United States, in the period 2003 to 2013, coronary mortality and stroke mortality rates decreased in relative terms by 28.8% and 33.7%, respectively.[2] Despite these impressive reductions in cardiovascular mortality in recent decades, ASCVD not only remains the main preventable cause of morbidity and mortality in developed countries but has also become the main cause of morbidity and mortality in developing countries.[3]

The current European guidelines on cardiovascular prevention[4,5] recommend using a probabilistic tool that includes traditional cardiovascular risk factors to estimate the future risk of ASCVD. The widespread use of such risk scales is an attractive strategy, as it allows quantitative estimation of 10-year and 30-year cardiovascular risk in a simple, inexpensive, and easy way, while also providing information to help determine the most suitable treatment strategy.

Although risk scales are easy to use and provide quantitative risk measurement, it is important to recognize the inherent limitations of ASCVD in primary prevention in a large part of the population. Among them, the lack of accuracy that is inherent to applying scales derived from population-based risk models to individuals. Traditional scales do not take into account proven risk factors such as family history of premature coronary disease, previous treatment of risk factors (intensity, duration, and even adherence to statin use), variability in risk factor measurements, the magnitude of risk factors (ex-smokers), and length of exposure and variability of exposure to risk factors over time. Therefore, the widespread use of traditional risk scales significantly underestimates individual risk in many cases, leading to underuse of pharmacological treatments and lifestyle modifications.[6] Furthermore, most cardiovascular events occur in individuals classified as low or intermediate risk by conventional scales. Finally, most contemporary scales have not been prospectively validated for accuracy or capacity to reduce cardiovascular events.

PERSONALIZATION OF CARDIOVASCULAR RISK USING NONINVASIVE QUANTIFICATION OF SUBCLINICAL ATHEROSCLEROSIS

Unlike traditional scales based on probabilistic calculations derived from population-based studies, noninvasive imaging techniques such as coronary artery calcium scoring (CAC) and carotid ultrasound allow visualization and quantification of atherosclerotic burden. That is, they allow measurement of the cumulative effect of all the risk determinants of an individual over his or her lifetime and in the arterial territory of interest, which can be integrated with exposure to known and unknown risk factors. Personalization of risk by evaluation and quantification of atherosclerotic burden is considered the main advantage of noninvasive cardiovascular imaging; it generally provides a more accurate reflection of the complex biological interaction networks and multiorgan interconnectivity that underlie the enormously complex pathogenesis of atherosclerosis as a systemic phenomenon.[7] In fact, it has been repeatedly demonstrated that, in addition to traditional risk factors, CAC significantly improves the predictive power for ASCVD and the capacity to identify individuals who would benefit from intensive pharmacological therapy, such as aspirin and statins.[8]

Various population-based studies have found correlations between the presence and severity of atherosclerosis in different vascular territories,[9] allowing early detection in apparently healthy individuals' peripheral arteries, especially in the carotid arteries.

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Cardiovascular risk assessment by carotid ultrasound is based on the measurement of intima-media thickness (IMT) and the evaluation and characterization of atherosclerotic plaques. The relationship between IMT and cardiovascular disease is not linear. It appears to have higher predictive power in women than in men, lacks measurement and definition standards, and has high variability and low intraobserver reproducibility.[10] In a meta-analysis by Den Ruijter et al., the authors demonstrated no added value with the measurement of carotid IMT compared with the Framingham Risk Score (FRS) for prediction of future cardiovascular events, including the intermediate risk subgroup.[11] Therefore, it is unsurprising that both the 2013 American guidelines[12] and the recent 2016 European guidelines[4] no longer recommend its routine use in cardiovascular risk assessemnt.

Quantification of carotid plaque area using 2-dimensional ultrasound has been demonstrated to be more accurate than IMT, and a larger area is associated with increased risk of coronary and cerebrovascular events.[13]

USEFULNESS OF NONINVASIVE IMAGING IN FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia (FH) is a genetic disorder characterized by very high concentrations of low-density lipoprotein cholesterol (LDL-C), increased cardiovascular risk (up to 20 times) and premature cardiovascular disease. Coronary artery disease is the main cause of morbidity and mortality in individuals with FH.[14] The disorder is caused by mutations in 3 genes: the LDL receptor gene, the gene that codes for apolipoprotein B, and the gene that codes for the proprotein convertase subtilisin/kexin type 9 (PCSK-9). In practice, around 60% of patients with a clinical diagnosis of FH have no detectable mutation in any of these 3 genes: a polygenic cause has been proposed for the increased LDL-C concentrations in these patients.[15]

Identification of individuals with FH is complex, given that they have the genetic abnormality from birth with the associated increased LDL-C levels, yet remain asymptomatic until the onset of target organ damage. Therefore, affected individuals may come into contact with the health system when they become symptomatic, from an incidental LDL-C measurement, through a screening program that studies individuals based on familial association, or through population-based screening programs.

Stratification of cardiovascular risk in these individuals is complex: cardiovascular risk estimation scales such as SCORE or FRS are inappropriate for this population, given that individuals with FH are at considerably higher risk from exposure to high LDL-C concentrations throughout their entire lifespan. Furthermore, FH represents a widely heterogeneous group of genetic-based disorders, not only in terms of genotype, but also regarding expression of individual cardiovascular risk. This heterogeneity places a further practical limitation on the clinical management of these patients: although they are at increased cardiovascular risk, not all are at the same risk.

Primary prevention of ASCVD with early aggressive treatment of LDL-C concentrations and modification of other cardiovascular risk factors has demonstrated effectiveness.[14] Particularly in the current era, with the introduction of monoclonal antibodies in addition to existing therapies, clinical management demands a more accurate reclassification to help identify and prioritize such treatment strategies.

Therefore, in the context of FH, it is essential to study the predictive value of diagnostic modalities that allow quantification of atherosclerotic disease progress. Currently, there is no validated noninvasive imaging modality that predicts the prevalence and progression of atherosclerosis and cardiovascular events in asymptomatic individuals with FH.

Multiple studies have demonstrated the correlation between the presence of carotid plaques and FH.[16] The study presented by Bea et al. in *Revista Española de Cardiología*[17] represents a landmark, being the first to demonstrate the usefulness of carotid ultrasound in predicting "hard" events in a population with FH followed up prospectively for a mean of 6.26 years. The presence of carotid plaques was associated with an increased risk of cardiovascular events, 4.3 times higher than that in the absence of plaques and 2.4 times higher after adjustment for major risk factors.

The study has far-reaching implications, given that it demonstrated that visualization of carotid plaques in a population with FH (classified as high risk) correctly identified those patients at a higher risk of cardiovascular events. Accurate risk stratification in a population with such high– yet clearly heterogeneous–risk will allow standardization of criteria on treatment intensity and indication for combination therapy.

QUANTIFICATION OF CAROTID PLAQUE BURDEN: IS 3-DIMENSIONAL ULTRASOUND THE FUTURE?

The implementation of any innovation usually begins in subgroups of selected patients, well-defined as being in a specific disease stage or, more commonly, having a very high risk profile, as is the case of the study by Bea et al.

In recent years, several studies led by Valentín Fuster have explored the predictive value of a novel technique based on quantification of the 3-dimensional (3D) volume (rather than the area on 2-dimensional [2D] ultrasound) of the carotid plaque burden in predicting cardiovascular events.[18]

The BioImage study was a landmark in the use of noninvasive imaging techniques to increase accuracy in cardiovascular risk prediction. Baber et al. carried out a prospective study of an asymptomatic cohort (n = 7687; mean age, 69.6 years), with the aim of predicting atherothrombotic events in the near-term (3 years) using noninvasive imaging of 2 arterial territories: they assessed the total atherosclerotic burden in the carotid arteries using 3D ultrasound and CAC.[19] The study demonstrated that the carotid plaque burden on 3D ultrasound was comparable to CAC in predicting mortality, myocardial infarction, angina, and coronary revascularization, over a mean follow-up of 2.7 years.

Around 60% of the study population and half of those classified as low risk by FRS had an atherosclerotic burden on 1 of the 2 imaging techniques. Both CAC and 3D carotid ultrasound reclassified patients more accurately than FRS, with similar net reclassification indices. More than 40% of patients at intermediate risk according to FRS and 12% of all patients were appropriately reclassified by imaging techniques. In addition, both imaging techniques reclassified more than half the population with no events from the entire cohort of FRS categories as low risk (3152 when using CAC, or 2792 when using 3D ultrasound; of 5726 individuals). The results demonstrate that, in all risk categories, the presence of atherosclerosis in both arterial territories confers higher risk than single territory atherosclerosis. There was a gradient in risk between an increase in CAC and an increase in carotid atherosclerotic burden that persisted independently of the risk factors and of each imaging technique, affirming the incremental effect of systemic atherosclerosis on short-term cardiovascular risk.

CHALLENGES IN IMPLEMENTING NONINVASIVE IMAGING IN PREDICTION OF CARDIOVASCULAR RISK

What are the greatest challenges when using imaging to improve cardiovascular risk prediction? The first is the cost, the second is safety (in the case of CAC, radiation), and the third is patient selection. Last, and given that 80% of cardiovascular events

occur in countries with medium or high incomes, the ideal technique should be scalable and implementable in such regions.

Two-dimensional carotid ultrasound has been demonstrated to have high predictive power in various primary prevention cohorts, capable of reclassifying risk beyond traditional risk scale estimates; in the case of FH, it can identify patients at higher risk of cardiovascular events, who should receive combined, high-intensity, high-dose treatments.

Visualization of carotid atherosclerotic burden and measurement of plaque volume using 3D ultrasound provides a noninvasive imaging tool with a predictive power similar to CAC but without any health risk to patients, who are not exposed to radiation; it can be repeated, it is portable, scalable, and cheaper than CAC.

The future of cardiovascular prediction will undoubtedly involve 3D ultrasound. It is expected that improvements in this technique–in both the measuring capacity and the availability of online data processing–will be available in the near future. This will mean a greater capacity for atherosclerosis detection in early studies, more precise measurements, and the capacity to repeat studies to assess disease progress and treatment response.

Studies like BioImage will undoubtedly be pioneers in the application of noninvasive imaging techniques for the quantification and evaluation of atherosclerotic burden in population-based studies. Most studies that are underway are in populations older than 60 years. The atherosclerotic process in this age group tends to be well-established after decades of progression and may not be completely reversible. In this context, and to assess the onset and progression of atherosclerosis, the PESA study (Progression of Early Subclinical Atherosclerosis) will provide information from middle-aged populations.[20] PESA is a longitudinal study, coordinated by the CNIC (Spanish acronym for the National Center for Cardiovascular Research) in partnership with Santander Bank and the *Botín* Foundation, on the use of imaging techniques to detect the prevalence and progression of atherosclerotic disease in a population of 4500 Santander Bank employees between 40 and 54 years old, followed up for 9 years. Furthermore, the study will look at the association between clinical parameters and the presence of different genetic and epigenetic characteristics, metabolomics, proteomics, environmental factors, and health habits such as diet, physical activity, and sedentary lifestyle, and biorhythms.

Participants are assessed with basic imaging techniques, such as CAC, 3D ultrasound of the carotid arteries and 2D ultrasound of the abdominal aorta, and other more advanced techniques, such as cardiac magnetic resonance and positron emission tomography. The results of the PESA study, similarly to the study by Bea et al. published in *Revista Española de Cardiología*, are sure to more accurately establish the clinical usefulness of cardiovascular risk stratification with noninvasive assessment of the individual's atherosclerotic burden.

CONFLICTS OF INTEREST

None.

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