Let´s Improve Coronary Risk Prediction in Spain

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During the past decade, risk estimation has become a milestone in the guidelines of cardiovascular prevention for managing risk factors globally in clinical practice.[1] Cardiovascular risk establishes the probability of suffering a cardiovascular event within a period of time, generally 5 or 10 years.[1]

To calculate this risk, most workgroups have used estimations proceeding from the Framingham study.[2] Undoubtly, it is the cohort epidemiologic study with the longest follow-up that provides best information on cardiovascular risk factors and their role in predicting coronary events. Absolute risk calculation has clinical importance due to the following: *a)* it is a useful tool to identify high risk patients that require an intensive and early intervention; *b)* it helps motivating patients when abiding to pharmacological, hygienic and diet measures; *c)* it helps in modulating stress intensities depending on how risk evolves in the control of cardiovascular risk factors, and *d)* in primary prevention, it allows a better assessment when deciding if hypertensive or hypercholesterolemic therapy should be initiated in patients without any previous or present cardiovascular event.

It is also true that risk calculation based on the Framingham study has some limitations, perhaps the most important being that absolute risk in the Framingham population will not be necessarily the same in other populations. In fact, this data was proven to overestimate the risk in a Mediterranean population[3,4] and even in some Scandinavian populations,[5] while underestimating the risk in others, such as European individuals of African or Asian origin.[6]

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Coronary risk is calculated more frequently than cardiovascular risk in the guidelines for simultaneous treatment of arterial hypertension and hypercholesterolemia, as this first calculation is a reasonable approximation to the second in clinical practice. A simple method for calculating cardiovascular risk based on coronary risk is to multiply the second value by 1.3.[7] The Framingham study researchers considered a coronary event on of the following: a recently initiated angina, silent o clinically evident myocardial infarction, coronary failure or unstable angina and death due to coronary disease. The majority of tables include a risk calculation of all these events within the general meaning of ischemic heart disease. Only the adjusted table published by Grundy[8] estimates coronary risk in a more limited sense, considering all the concepts mentioned above except recently initiated angina. As with cardiovascular risk and coronary risk, an approximation can be found between both meanings. The ischemic heart disease risk in the strict sense, is approximately two-thirds in the wide sense.

An important aspect to be considered, not sufficiently discussed, is that coronary risk calculated using the Framingham tables is not totally equivalent to risk described in the results of primary prevention clinical trials. As an example, coronary disease in the form of myocardial infarction and sudden death is the main result defined in the clinical trials for arterial hypertension and hypercholesterolemia therapy. The limited coronary risk concept mentioned above includes more syndromes than coronary disease risk defined in clinical trials. When extrapolating the risk of placebo-controlled group clinical trials to the general population, what is frequently done to issue recommendations about risk factor management, we should consider that any estimation calculated using the tables will be higher than the actual risk for one group. If an ideal method for calculating cardiovascular or coronary risk could be chosen, it should fulfill the following conditions:

1. The total cardiovascular risk should be obtained: as hypercholesterolemic or antihypertensive therapy will effectively reduce coronary disease and cere-

brovascular disorders, the ideal method should calculate cardiovascular risk and not only coronary risk.

2. It should be based on the Mediterranean population: absolute risk depends on the risk of suffering a cardiovascular disease of a population. It is known that Spain presents a very low ischemic heart disease mortality rate with an intermediate cerebrovascular disorder mortality rate, compared with other countries. The geographic peculiarities of risk factors and how the diseases are distributed requires specific methods for each population.

3. It should consider cholesterol binded to high density lipoproteins (HDL-C): this is extremely important, as HDL-C values in the Spanish population are different than in certain tables. As an example, the tables proposed by the European societies were elaborated using HDL-C fixed values of 39 mg/dL for males and 43 mg/dL for females. This is somewhat lower than the average described for the Spanish population, actually 48 mg/dL for males and 58 mg/dL for females.

4. Diabetes should be included as a risk factor. There are several arguments towards and against categorizing diabetic patients with an equivalent ischemic heart disease risk. A number of observational studies, but not all of them, include information about equal risks for diabetic and myocardial infarction patients. While this controversy is not settled, it is advisable to consider diabetes as another risk factor.

5. Finally, the ideal method should be easy to apply in clinical practice.

Currently, the most frequently used method in Spain that resembles the ideal method depicted above is the Anderson table,[2] based on the Framingham study. It does not calculate cardiovascular risk but total coronary risk, although the result is a practical and reasonable approximation that the European societies also propose.[1] This table includes the following risk factors as quantitative variables: age, gender, total cholesterol, systolic blood pressure and HDL-C. Diabetes mellitus, smoking and left ventricular hypertrophy are considered as binary variables.

Marrugat et al[9] publish an article in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA about coronary risk estimation. It is also an approach to the main limitation of the Framingham tables mentioned above. Actually, it proposes risk calculation tables based on the Framingham study that are calibrated by replacing risk factor prevalence and coronary event incidence rates with data obtained from the REGICOR study. This study compares the <19% risk percentage of individuals to 10 years using the classical and the calibrated function with noticeable results. Total percentage is 13 times lower when the calibrated function is used. Applying these results practically, in opinion of the authors, could specially influence the treatment of hypercholesterolemia. A limitation of this study is that calibration was realized with data from a risk factor prevalence study and the population registry. Although the data was collected from the same population base, we cannot establish *sensu stricto* that populations were identical. Another limitation mentioned by the authors is that angina and silent AMI incidence rates had to be estimated with the proportions of the Framingham study. In consequence, the results cannot be simply extrapolated to Spain, as AMI incidence in Girona is nearly 15% less than the Spanish average. Nevertheless, this study is a strict approach with calibration results to be considered, although an appropriate prospective validation is necessary, as the authors mention in their article.

There is a European project named SCORE (Systematic Coronary Risk Evaluation),[10] which results are soon to be published in the *European Heart Journal*. It presents European risk calculation tables based on 12 European cohorts of 205,178 individuals that represent 2.7 million persons per one year follow-up, with 7934 cardiovascular deaths of which 5652 deaths were caused by coronary disease. These tables are to be included in the next European cardiovascular prevention recommendations, that will instigate important changes. The Framingham tables, a worldwide historical reference recommended since 1994 by the European societies, will cease to be recommended. An advantage of the future European tables, already presented by the researchers at several conventions, and their difference with the Framingham tables, is that they are based on fatal events exclusively, what allows total cardiovascular risk estimation. They also offer the possibility of obtaining tables for high and low risk European countries, and tables for coronary, cerebrovascular and cardiovascular events separately. Some of their aspects are subject to debate, as mentioned by Marrugat el al. Non-fatal events are discarded, what disrupts the purpose of primary prevention risk calculation in clinical practice, that is to identify patients not only with a high risk of death, but also patients at risk of suffering cardiovascular events with sequels affecting quality of life. To this respect, the SCORE Project researchers mention that the Framingham study non-fatal event definition is different in the majority of cohort studies and clinical trials. This would render the validation of risk function in other studies a difficult task.

We should also mention the ERICE Project,[11] one of the recent cooperative research thematic networks financed by the Instituto Carlos III of the Ministry of Health, that will jointly analyze data collected from 9 cross-sectional studies (a population of over 23 000 persons), amongst other targets. A cohort will be created from the cross-sectional studies, and the minimum 5 years follow-up will be completed for those studies where it is not included, to obtain information both of fatal and non-fatal events. This could be a way of ob-

taining a genuine Spanish risk calculation equation in the future.

With all these initiatives, we will undoubtly improve risk calculation accuracy in Spain, as it has proven a useful tool in cardiovascular disease primary prevention, specially in primary health care. We should also admit it will never be a perfect tool for identifying high risk patients, and that probabilities will always exist, as some patients with multiple risk factors never suffer a cardiovascular event, while others without any of the risk factors commonly included in the tables do. It is already known there are other cardiovascular disease related risk factors that are not included in risk calculation, such as obesity, sedentarism, a family history of early coronary disease, hypertriglyceridemia, small and dense LDL, the (a) lipoprotein, fibrinogen, homocisteine, inflammatory factors, psychological and social factors, and possibly others. This does not mean they should be omitted, but considered within each patient´s clinical context. In the future, genetic prediction of coronary disease by analyzing certain genotypes will have an important role in predicting coronary risk.

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