Reflections on Cardiovascular Risk Estimates in Primary Prevention

To the Editor:

We believe that some of the arguments by Grau et al in a recent article deserve reflection:

1. In order to emphasize the usefulness of coronary risk functions on lipid-lowering treatment, they maintain that they have only demonstrated
its efficacy in primary coronary prevention, but not on the reduction of cerebrovascular accidents (CVA), while recent meta-analyses\(^1\) have analysed the evidence on primary and secondary prevention separately with results that confirm their favourable effect.

2. They sustain that the coronary risk calculation is preferable to the cardiovascular risk calculation since this involves “overtreatment.” However, all of the recent prestigious clinical guidelines (societies, NICE, etc) recommend using cardiovascular risk for stratification in primary prevention, though they later differ in the methodology.

3. In diabetics, they confirm that VERIFICA\(^1\) has demonstrated that the adapted REGICOR function (RF) “precisely” estimates the rate of coronary events at 5 years, which is true. But does this mean it is clinically sufficient? The answer does not need to be negative, since one factor is “precision” and the other, which is defined as “reliability” or classificatory validity, is what is clinically interesting. The VERIFICA study does not provide data on sensitivity and specificity; however, other studies do with discouraging results.\(^4\)

4. After years of insisting on the overestimation of risk by the Framingham function (FF), the VERIFICA study comes along and confirms the hypothesis\(^5\) that would justify its use in our environment. The FF, though overestimating risk on population, maintains its limited validity for classification. Calibration of the RF substantially improves the populational predictive validity, but it barely changes the classificatory validity in terms of sensitivity and specificity. Therefore, the relevance of its clinical use is not to use one or the other but rather to define a cut-off point.

5. The choice of the cut-off point is biased, in our opinion, towards reducing spending. For Comín et al\(^6\) using data from VERIFICA, the RF (cut-off point >10%) obtained a sensitivity of 36.8% and a specificity of 78.5% for coronary events; for the FF (cut-off point >20%), these values were 57.3% and 78.5% respectively. But, which one is preferable: a sensitivity of 36.8% with a specificity of 88.3% (we treat a few patients but the reach of primary prevention will be more limited) or a sensitivity of 57.3% with a specificity of 78.5% (we treat more patients but we avoid more events)? Using their data and assuming that statin treatment reduces coronary events by 33% (New Zealand guidelines), the differences in clinical efficiency are much less (NNT=28 with FF and NNT=34 with RF) than the differences in the percentage of population identified as high risk (22.4% with FF vs 12.4% with RF). Stratification of risk is crucial for adequate primary prevention, but there needs to be a review in which there is sufficient debate on the reason for choosing a given concept and the method for calculating, as well as the possible practical results of the proposed cut-off points.

Salvador Lou Arnal and Ángel Vicente Molinero
Servicio de Medicina Familiar y Comunitaria, Centro de Salud Utero, Zaragoza, Spain

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Response

To the Editor:

We appreciate the comments by Lou and Vicente on the review “Risk Functions and the Primary Prevention of Cardiovascular Disease.”\(^2\) We will gladly discuss some of the opinions that the authors stated in their letter.

On the first 2 points, the PROSPER\(^3\) and ALLHAT\(^3\) studies with a majority of patients over 65 years of age, in which the major concentration is on cerebrovascular disease (CVD), statins did not demonstrate any benefit. Both meta-analyses have shown that these drugs reduce absolute risk for CVD (by 0.7%) and ischaemic heart disease (IHD) (by 2%) with number needed to treat (NNT) of 268 and 60 patients respectively.\(^4\)\(^5\) One meta-analysis is a statistical technique that is subject to many limitations which cannot be substituted, under any circumstance, with the results of an adequately designed clinical trial. No clinical trial has demonstrated that the use of lipid-lowering drugs
would be effective in primary prevention of CVD. The uncritical application of the meta-analyses results, of doubtful clinical significance (though statistically significant), in the primary prevention of CVD leads to overtreatment of the population. On the other hand, emphasis should be placed on treatment and control of hypertension, whose contribution to the risk of CVD is much greater. It is reasonable to optimise prevention efforts, focusing on the use of statins by estimating coronary risk, which has demonstrated its efficacy in clinical trials on primary prevention. This is not “economism” but rather clinical-epidemiology based on scientific studies.

Regarding diabetics (third point), the VERIFICA study demonstrated that prediction by the adapted REGICOR function did not differ significantly from real everyday practice (rate of incidence of coronary events), but it did not include those which refer to discrimination (sensitivity and specificity using an ROC curve) due to questions of space. We gladly include these data in Figure. According to these data, it should be pointed out that despite correctly discriminating the REGICOR function, the results for discrimination are somewhat worse (not “disappointing”). In the near future, we expect that the addition to the function of variables such as time since onset, metabolic control, or microalbuminuria will improve both characteristics.

In the fourth and fifth points, Lou and Vicente argue that the important point is not which function to use, but rather the choice risk header. This is incorrect. As we have argued in the review, each country must use the function that is most accurate in making a prediction. Faced with a risk of 20% using the Framingham formula, we can feel vindicated in making aggressive prevention decisions that have a REGICOR equivalent of approximately 8%. However, the real risk in Spain is 8%. The cut-off points must be established by consensus among experts in the real risk and not based on overestimated risks. We do not believe that these criteria can be considered to be “economism” but rather “veracity” of the estimation.

Lou and Vicente mistake the first appearance of 78.5% (specificity) since it should have been 88.3%. We do not know either how to estimate the NNT with a relative risk reduction of 33%, since the calculation must be made using the absolute reduction of risk.

In a country with a low incidence of myocardial infarction such as Spain, it appears to be more reasonable to be stricter with the specificity than with the sensitivity, in order to avoid unnecessarily treating the population that does not need it. In the future, screening for cardiovascular risk in the population will include new markers combined with advanced imaging techniques in order to provide a better approximation of the long-sought perfect sensitivity and specificity.

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3. The ALLHAT officers and coordinators for the ALLHAT collaborative research group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT). JAMA. 2002;288:2998-3007.