

The challenge of risk prediction: How good are we?

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Guidelines make recommendations based on results mainly deriving from major randomised clinical trials (RCTs), with the aim of applying such recommendations to the general population. In the current issue of *European Journal of Preventive Cardiology*, Pavlovic et al.¹ evaluated how the 2013 American College of Cardiology (ACC)/American Heart Association (AHA)² and 2016 European Society of Cardiology (ESC) guidelines for the prevention of atherosclerotic cardiovascular disease (ASCVD)^{3,4} may be applied in a population seemingly free of ASCVD; they evaluated the eligibility of each subject included in the Rotterdam study for 11 RCTs on statin, based on inclusion and exclusion criteria of each RCT.¹ A high variability in the proportion of the population eligible for each trial was observed, ranging from 0.4% up to 30.8%, some individuals being eligible for more than one RCT.¹ A significant divergence between the two guidelines in the proportions of subjects who would receive a definite positive recommendation for lipid-lowering treatment was observed.¹ The authors concluded that, contrarily to RCTs done in patients with high cardiovascular risk, RCTs targeting low-to-intermediate risk subjects are less represented in the guidelines, particularly in the ESC recommendations.¹

Certainly, the attempt to stratify subjects in primary prevention who are free of ASCVD is a difficult one. All approaches to risk scoring have their problems based on the population studied, the type of events considered, and the factors contributing to risk that have been followed. In addition, stratification is complicated by concomitant factors that are contributing to the risk stratification. The ESC guidelines address this issue by suggesting a number of clinical and subclinical conditions that contribute to risk by increasing the score and/or 'promoting' the patients to secondary prevention.⁵ Furthermore, both the ESC/ European Atherosclerosis Society (EAS) and ACC/AHA guidelines exclude diabetics and those with severely elevated low-density lipoprotein cholesterol (LDL-C) levels above 190 mg/dl from risk determination tools to determine the indication for lipid-lowering therapy since these patients are automatically at high risk. In the

ESC guidelines, the presence of significant subclinical atherosclerosis and chronic kidney disease is also considered a very high-risk category. Several of these conditions were not taken into account in the Rotterdam study. We therefore believe that the power of requesting a therapy is rather underestimated in the present article.¹ Just because of this, the statements of the authors are probably overestimating the failures of the scoring approaches.

Another point, to which attention should be focused, is the need to recalibrate current guidelines for each specific country based on national databases. This would allow an increase in the possibility of better categorising cardiovascular risk, taking into account factors that may differentially affect the determination of cardiovascular risk in different countries. The authors have used the low-risk country SCORE calibration method which may have limitations for the populations applied. The health economics and side-effects aspects of covering a large primary prevention cohort with statins should also be taken into consideration.

This is not to downplay the limitations of the currently used scoring systems, which are large and require refinement. Leveraging on the genetic information obtained from genome wide association studies (GWAS) studies will inform us on how to better approach these limitations, and the under-treatment of younger subjects owing to the fact that many risk calculators have a 10-year perspective. This perspective is, by definition, limiting the power to detect the long-term effect of increased levels of risk factors. Genetic studies are providing evidence that the maintenance of lower LDL-C levels throughout life is more useful than giving statins to patients for secondary prevention of

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atherosclerotic vascular disease. Therefore, it will be extremely useful to define the subgroup who will derive the best benefit/risk ratio. It becomes of utmost importance to focus on primordial prevention to prevent huge numbers of people becoming candidates for pharmacotherapy.

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