Journal Pre-proof

Is the cardiovascular risk SCORE2 globally valid and useful?

Ana Abreu

PII: S0870-2551(24)00186-0

DOI: https://doi.org/doi:10.1016/j.repc.2024.06.001

Reference: REPC 2342

To appear in: *Revista Portuguesa de Cardiologia*

Please cite this article as: Abreu A, Is the cardiovascular risk SCORE2 globally valid and useful?, *Revista Portuguesa de Cardiologia* (2024), doi: https://doi.org/10.1016/j.repc.2024.06.001

Is the cardiovascular risk SCORE2 globally valid and useful?

SCORE2 de Risco CV: Válido e Útil Globalmente?

Ana Abreu[1,2]

[1]Unidade de Prevenção e Reabilitação CV, Serviço Cardiologia, Hospital Santa Maria/ULS Santa Maria e Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal

[2]Instituto de Medicina Preventiva e Saúde Pública e Instituto de Saúde Ambiental da Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal

E-mail address: ananabreu@hotmail.com (A. Abreu)

Atherosclerotic cardiovascular (CV) disease (ASCVD) is known to be a major cause of mortality and morbidity worldwide.[1] There have been many advances in treatment over the years, including invasive percutaneous coronary intervention, and secondary prevention with statins, other lipid-lowering agents and new antiplatelet agents is in widespread use, with prognostic impact.[2,3] However, in the population not diagnosed with CV disease (CVD), a major issue remains in practice: how to assess CV risk, which could enable primary prevention of ASCVD, acting upstream. Most CV events can be prevented by control of behavioral risk factors, such as unhealthy diet, smoking, obesity, physical inactivity, and excessive alcohol consumption.[4]

Various risk prediction models and scores have been created over time,[5] but the application of these models to other countries or continents continues to pose considerable challenges.[6]

Regarding the Portuguese population, the few CV risk studies that have been conducted were restricted to specific subpopulations. In order to classify the CV risk for each population, providing a valid and efficient risk prediction model is a high priority: overestimation of risk can result in higher treatment and intervention costs, while underestimation can lead to the underuse of preventive measures in moderate- or high-risk cases.[7]

SCORE (Systematic COronary Risk Evaluation), a CV risk score for apparently healthy people that only estimates 10-year CV mortality, was initially developed in 2003.[8] In the 2021 European Society of Cardiology (ESC) guidelines on CVD prevention,[9] SCORE was replaced by SCORE2,[10] which is based on updated risk prediction algorithms and besides mortality includes non-fatal events such as myocardial infarction and stroke, and was extended to older patients with SCORE2OP (Systematic COronary Risk Evaluation 2 Older People). The authors of SCORE2 demonstrated that it estimates the total burden of CVD, particularly among younger individuals, better than the previous SCORE, as well as showing better

risk discrimination. The use of SCORE2 can be considered clinically relevant as it means that, in this version, higher-risk patients with subclinical atherosclerosis can benefit from earlier and more rigorous CV risk management strategies to prevent future CV events.

The data from different countries used to determine SCORE2 did not include the Portuguese population, meaning that risk estimates cannot necessarily be extrapolated to this population. Accordingly, in their article published in this issue of the *Journal*,[11] Temtem et al. decided to compare SCORE with SCORE2 and to validate the use of SCORE2 in the Portuguese population. This well-structured study emphasizes the need to validate SCORE2 in Portugal, as well as in other populations in which the previous models may not have been totally representative. A good number of CV risk factors, including demographic, clinical and lifestyle variables, were assessed. This broad approach increased the study's ability to accurately assess the impact of these factors on CV risk.

The study included 1071 individuals (age 57.2±6.1 years; 75.2% male) without CVD or diabetes (selected from the GENEMACOR study controls[12]), stratified into the three risk categories used by SCORE2, and assessed over a period of 5.4±3.9 years (range 0.8–19.3 years). The authors concluded that SCORE2 improved CV risk stratification in this population, with a significant advantage in identifying patients with low-to-moderate, high or very high risk of CV events, and that the updated SCORE2 algorithm demonstrated strong predictive ability and effective CV risk discrimination for all groups in the middle-aged population of the Portuguese island of Madeira.

At this point, several issues in the study[11] deserve to be highlighted:

- Follow-up duration: In reality, several patients were not assessed at 10 years, which is the time considered for risk estimation, and several were assessed after less than five years. The highest-risk group had an event-free survival probability of 72%, while for the lowest-risk group this was 99%. The intermediate category had a 90% event-free survival likelihood ($p<0.0001$). What figures would be found if all patients had been followed for 10 years? Is it valid to extrapolate the results for 10 years?

  It is a common practice in epidemiology to extrapolate events in time; however, this approach has important methodological implications and requires the use of appropriate statistical techniques to ensure validity. Additional details on the process of data extrapolation and consideration of changes in risk patterns could have been included, which would have enriched the discussion and strengthened the validity of the study's conclusions. The representativeness of 721 participants with 10 years of

follow-up is not guaranteed simply because this was a significant part of the total sample. It depends on how these patients reflect the diversity of the total population, in demographic, clinical and behavioral terms. There could even have been survival bias, in which those with better health status tended to remain in the study for longer.

- Portuguese representativeness: The Portuguese population was represented in this study by only one single-center population sample from the island of Madeira, which means that there could be differences relative to mainland Portugal. Ideally, the study should have included Portuguese people from different regions of the country. Some questions may remain: Can we consider the results representative of the whole country? Are the incidence and standardized mortality for CVD in the island of Madeira similar to the overall Portuguese population? How were the individuals recruited?
- Gender discrepancy: Unlike SCORE2, based on 677 684 participants of whom 66% were female and mean age was 57±9 years, in this Portuguese population sample, as in many other studies, fewer than 25% were women, so the female population sample size was underestimated, meaning that it was impossible to discriminate the specific risk in females (small sample subgroup of fewer than 300 women).

In summary, the main differences regarding the Portuguese cohort from Madeira analyzed in this study[11] were the length of median follow-up (5.4±3.9 years vs. 10.7 years in SCORE-2), the use of a single hospital center in Madeira, and the small percentage of women included (24% vs. 66%), relative to the SCORE2 population.

However, despite some limitations, this well-conducted study, one of very few on CV risk in Portugal, provides a closer look at fatal and non-fatal CV risk in part of the Portuguese population. This important study addresses the need for accurate tools for risk stratification regarding CV events in those without known CVD, one of the most common causes of morbidity and mortality worldwide. Its results have important implications for CV risk assessment in Portugal, supporting the generalized use of SCORE2 in clinical practice for more precise and effective public health interventions.

Thus, in my view, the idea of baseline risk and how it is to be modified should be changed, by raising awareness in health professionals and improving the education of the general population. The use of the same tools to quantify risk enables CV risk to be compared between countries, elucidating how we are doing in relation to others and learning from those with the most effective strategies. This important information can support many health information campaigns. The support of models that predict the

impact of public health interventions and of quality care in reducing CV events in the medium term is essential in health systems. Integrated multidisciplinary support strategies for populations and individual CV risk reduction are needed, as is the organization of person-centered care,.

Despite the important role scores can have, I would say that to assess the risk of populations, important risk factors, including environmental, social and psychological variables, should not be ignored, although they have so far not been included in the algorithms. It is interesting to note that, for the first time, the updated 2021 ESC guidelines[9] address the impact of environmental factors, including water, air, and soil pollution, on the risk of ASCVD.

Finally, machine learning-based classification can surely help to identify those at risk, and at higher risk, who may benefit most from early clinical decisions. This method improved risk prediction in 473 611 participants in a UK biobank cohort with 10 years of follow-up outcome data.[13] Also, in the future, genetic profiling will be applied to large-scale databases, including health care data. CV risk alleles will also be included, as part of the development of polygenic risk scores. These scores should be useful in the future to optimize CV risk prediction tools.[14] Integration of variables in conventional risk prediction models with additional risk markers, including imaging, biomarkers and genetic data, together with advances in the field of artificial intelligence, will be an emerging issue for CV risk prediction in the future.[7,14] Artificial intelligence and big data analysis are already a reality and very soon new algorithms will identify phenotypes of CV and overall risk in different populations, making it possible to personalize prevention for subgroups, in a real model of precision medicine.

References

1. Mathers CD, Loncar D. Updated projections of global mortality and burden of disease, 2002–2030: data sources, methods and results. Geneva: World Health Organization; 2005.
2. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol 2020;28:460–495. https://doi.org/10.1177/2047487320913379 717.
3.Abreu A, Frederix I, Dendale P, et al. Standardization and quality improvement of secondary prevention through cardiovascular rehabilitation programmes in Europe: the avenue towards EAPC accreditation programme: a position statement of the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology (EAPC). Eur J Prev Cardiol 2020;28: 496–509. https://doi.org/10.1177/2047487320924912
4. WHO. Global action plan for the prevention and control of NCDs 2013-2020. Available online at:

https://www.who.int/publications/i/item/9789241506236

5. Sofogianni A, Stalikas N, Antza C, et al. Cardiovascular Risk Prediction Models and Scores in the Era of Personalized Medicine. Journal of Personalized Medicine. 2022; 12(7):1180. https://doi.org/10.3390/jpm12071180
6. Choi J., Sung S., Park S., et al. SCORE and SCORE2 in East Asian population: a performance comparison. JACC Asia. 2023 Dec 26;4(4):265-274
7. Krittayaphong, R. Cardiovascular Risk Prediction Model in Asians: Current Status and Future Direction. JACC Asia. 2024 Mar 19;4(4):275-278.
8. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003 Jun;24(11):987-1003. doi: 10.1016/s0195-668x(03)00114-3. PMID: 12788299.
9. Frank L J Visseren, François Mach, Yvo M Smulders, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC), European Heart Journal, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337, https://doi.org/10.1093/eurheartj/ehab484
10. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe, European Heart Journal, Volume 42, Issue 25, 1 July 2021, Pages 2439–2454, https://doi.org/10.1093/eurheartj/ehab309
11. Temtem M, Mendonça MI, Santos M, et al. Validation of the SCORE2 risk prediction algorithm in a Portuguese population: A new model to estimate 10-year cardiovascular disease incidence in Europe. Rev Port Cardiol. 2024 Feb 21:S0870-2551(24)00066-0. English, Portuguese. doi: 10.1016/j.repc.2023.10.011. Epub ahead of print. PMID: 38395299.
12. Mendonça MI, Pereira A, Monteiro J, et al. Impact of genetic information on coronary disease risk in Madeira: The GENEMACOR study. Rev Port Cardiol. 2023 Mar;42(3):193-204.
13. You J., Guo Y., Kang J.J., et al. Development of machine learning-based models to predict 10-year risk of cardiovascular disease: a prospective cohort study. Stroke Vasc Neurol . 2023;8:6: 475-485.
14. O'Sullivan J.W., Raghavan S., Marquez-Luna C., et al. Polygenic risk scores for cardiovascular disease: a scientific statement from the American Heart Association. Circulation . 2022;146:e93-e118.