Rev Port Cardiol. 2016;35(1):15–18

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

Cardiovascular risk scores: Usefulness and limitations☆

Scores de risco cardiovascular: utilidade e limitações

Evangelista Rocha

Serviço de Cardiologia, Hospital das Forças Armadas – Pólo de Lisboa, Lisboa, Portugal

Available online 25 January 2016

Prediction of cardiovascular (CV) risk is an aspect of CV prevention that has seen significant developments in recent years. The aim is to identify the main risk factors and markers that are potential therapeutic targets and to promote the implementation of cost-effective diagnostic and prognostic strategies in primary and secondary prevention of CV disease.

The article by Paredes et al. in this issue of the *Journal* on specific aspects of statistics and information technology is an important contribution to improving risk scores for secondary prevention.[1] It clearly demonstrates the need for collaboration between statisticians and clinical researchers in the development and validation of risk prediction models. The subjects in the study were patients in Hospital de Santa Cruz, a reference center due to the quality of its interventional care, especially coronary angiography and myocardial revascularization. This could be a source of selection bias, but the data on validation of the risk scores reveals that the study sample included the full spectrum of non-ST-elevation acute coronary syndromes (NSTE-ACS).[2] The new approaches analyzed in the study are able to cope with missing risk factors, which is a way to avoid excluding cases, although the authors recognize that care should be taken when extrapolating the results. Another important question is the frequency of the endpoint used to determine the sample size, rather than the total number of patients; a simple and practical method requires at least 10 events per variable, i.e. the number of patients with the endpoint divided by the number of predictive factors under study,[3] and by this method, the frequency of the combined endpoint was low (n=33). The approaches analyzed by Paredes et al. were validated by k-fold cross-validation, a method for assessing the ability of a model to make generalizations on the basis of a dataset. Using techniques from artificial intelligence, the authors performed optimization with genetic algorithms (the most popular of the larger class of evolutionary algorithms), which are among the CV risk assessment tools currently recommended by US and European medical societies (albeit without significant effect to date).

With regard to the usefulness and limitations of CV risk scores and their application in clinical practice for primary and secondary prevention, it is worth examining what we know and what remains to be clarified. First, healthy attitudes and behavior, which can be encouraged by low-cost measures both on a population-wide scale and aimed at high-risk patients, can render CV risk stratification unnecessary for many. However, CV risk must be assessed when it comes to clinical decisions and interventions, not only after CV events but also to prevent them from occurring in high-risk individuals.

The evolution of the Framingham Heart Study is illustrative. Following its establishment more than six decades ago in 1948, the project introduced the concept of risk factors in 1961, developed the first formulas for predicting various CV complications and algorithms stratifying risk factors for coronary artery disease in individuals without clinical manifestations of disease in 1998, and published other algorithms to estimate global CV risk and risk of CV events (coronary and cerebrovascular events, peripheral arterial disease and heart failure) in 2008.

DOI of original article:
http://dx.doi.org/10.1016/j.repce.2015.12.017

☆ Please cite this article as: Rocha E. *Scores* de risco cardiovascular: utilidade e limitações. Rev Port Cardiol. 2016;35:15–18.

E-mail address: evangelistarocha@hotmail.com

The need to adjust CV risk estimates to populations other than the original Framingham cohort (5127 men and women aged between 30 and 62) led to the development of other scoring systems, including PROCAM,[4] SCORE,[5] QRISK,[6,7] and the Reynolds risk scores for women and men.[8,9] Differences between these systems explain the variation in their risk estimates, but since 2003 the scoring system recommended by the European Society of Cardiology (ESC) has been SCORE.[5,10]

Since that date, Portugal has been classified among the low-risk countries. How is a low-risk country defined? In the ESC guidelines, the cut-off points are based on 2008 CVD plus diabetes mortality in those aged 45–74 years (220/100 000 in men and 160/100 000 in women). However, these cutoffs for classification of CV risk and therapeutic recommendations are to some extent arbitrary, since risk is a continuum, and some authors have found that SCORE performs less well in certain populations, giving rise to some controversy.[11,12] Risk estimation is not an exact science; in the Cox proportional hazards models often used, the regression coefficients are assumed to remain constant over time and in the context of different combinations of risk factors, but they do in fact vary as a person ages,[13] especially predisposing factors that aggravate independent factors. Explanatory variables are considered to act multiplicatively on the hazard function. At best, these assumptions and suppositions, and the different combinations of risk factors that interact in complex ways, are difficult to model, and so the models and estimates used are only approximations to 'truth'.[14]

The SCORE system assesses the 10-year risk of fatal cardiovascular disease (mortality from myocardial infarction [MI], stroke, aortic aneurysm or other). The choice of CV mortality, as opposed to fatal and nonfatal events, was deliberate, because nonfatal event rates are highly dependent on the definitions and detection methods used and are thus difficult to calculate accurately, especially in different study cohorts with long follow-ups. At the same time, basing the score on mortality enables calibration to take into consideration long-term trends in CV mortality. All risk estimation systems will overestimate risk in countries in which CV mortality has declined and underestimate risk if it has increased. However, recalibration should be undertaken if good quality, up-to-date mortality and risk factor prevalence data are available.[15] Even so, the inability of the SCORE system to differentiate the 10-year risk of a fatal event due to ischemic heart disease or due to stroke in individuals aged 40–65, or the risk in older individuals, since the risk profile of each disease is different, is a limitation; for younger individuals, in whom the absolute risk is low, the relative risk table is applied as a way of encouraging healthier lifestyles.

The recently published SCORE O.P.[16] is the first CV risk assessment system developed specifically for older individuals (≥65 years), both men and women. It shows good discrimination, with a low false positive rate, and may reduce excessive use of medication in older people without a history of CV events. The methodology excluded subjects with missing data on any of the required covariables, but simulated external validation was performed using cross-validation to assess the model's ability to generalize the 10-year risk function. The next step is to confirm the discriminative ability of the simulated external validation by widening the validation process using external datasets, before it is made available online and included in the ESC guidelines on cardiovascular prevention.

In the search for ways to improve CV risk estimation for secondary prevention, after various unsuccessful attempts, it is unlikely that a major new risk factor will be identified that is demonstrably linked to causality, or that the range of known polymorphisms will fill the gaps in risk prediction. It can be a challenge to use HeartScore, the online version of the SCORE risk charts (available at www.escardio.org), in the right way. Alternatively, the SCORE system needs to be calibrated, as has been done for some countries, so that the risk estimation model reliably predicts the level of absolute risk that is subsequently observed.

In terms of secondary prevention, the number of published articles assessing risk stratification models for acute coronary syndrome (ACS) demonstrates the extent of interest in this subject. One of the aims of clinical prediction models is to estimate the likelihood of an event after diagnosis of the disease (prognosis) in individual patients and to assist in clinical decision-making. Some ACS need rapid diagnosis and entail critical therapeutic decisions by health professionals with different levels of knowledge and experience, sometimes with limited resources. To this end, various risk models and scores have been developed to identify patients in emergency departments or coronary care units who are most likely to benefit from an invasive approach.

The best-validated risk scores were based on different populations in clinical trials (TIMI[17] and PURSUIT[18]) or registries (GRACE[19] and GRACE 2.0[20]). For NSTE-ACS, the GRACE score provides the best stratification of ischemic risk at hospital admission and discharge,[2,21] and – like the GRACE 2.0 score – is accordingly included in the ESC guidelines.[22,23] An invasive strategy (coronary angiography and revascularization) is recommended within 24 hours for a GRACE score >140 (high risk) and within 72 hours for a score >109 and <140 (intermediate risk). The original GRACE score, based on a six-month follow-up and validated for ACS with and without ST-segment elevation, was calculated on the basis of eight independent risk factors, giving a maximum score of 372. The PURSUIT score for unstable angina/non-ST-elevation MI predicts the 30-day incidence of death and the composite of death or MI, but only uses five predictive variables. The TIMI score is calculated on the basis of seven variables predicting severe complications (all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization) within 14 days of admission. It suffers from the same limitation as others based on clinical trials in which high-risk patients were excluded, but the TIMI score has shown good prognostic ability. However, in a multifactorial disease like atherosclerosis, these scores are largely determined by the patient's age, which makes it difficult for the physician to interpret an individual score.[24] Furthermore, the trials were designed with a short follow-up, limiting analysis of survival and of its implications. The recently updated GRACE 2.0 score estimates risk of death or MI in ACS from the acute (in-hospital) phase to 6 months, 1 year and 3 years.[21] The size of the patient cohorts is worthy of note: 1-year outcomes were derived from the dataset of 32 037 patients from the GRACE registry enrolled between January 2002 and December 2007, and 3-year mortality from the UK cohort of 1274 patients. The analysis, which used Cox multiple regression models, included the same indepen-

dent predictors of outcome as the original version, but also employed non-linear associations of the continuous variables of systolic blood pressure, pulse, age and creatinine, which improved model discrimination compared to the original. In addition, a simplified version of the risk score was developed with substitutions for creatinine and Killip class (history of renal dysfunction and diuretic usage, respectively), which performed almost as well, enabling physicians to assess risk in a wider range of ACS patients.

Cost-effectiveness analyses may reveal whether an improvement in performance is sufficiently important to justify measuring another variable in clinical practice. Although many potential markers have been studied in recent years, no new predictors have been identified that have a sufficiently large effect to identify patients with or without the endpoint. This is hardly surprising, given that validation of the GRACE model revealed that the model of only eight factors conveyed more than 90% of the predictive accuracy of the complete multivariable model.[19]

While the value of risk scores as tools to assess prognosis is inarguable, their impact on patient outcomes has not been adequately investigated.[25,26] Risk scores are undoubtedly useful, and they are simple to calculate using web-based calculators or portable apps. However, the literature reveals that risk scores are not applied systematically for risk management in ACS, despite the evidence and the guidelines. There are various reasons for this, including the mistaken idea that clinical assessment and the measurement of individual markers are sufficient.[27]

Gaps in knowledge for both primary and secondary prevention concerning the risk of CV events in both the short and the long term in ethnic minorities and different age-groups and genders mean that there is room for improvement. Systematic collaboration between statisticians, epidemiologists and clinical researchers, including cardiologists and internal medicine specialists, will lead to more rigorous methodologies and improve the quality of risk prediction models in CV research.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Paredes S, Rocha T, Mendes D, et al. New approaches for improving cardiovascular risk assessment. Rev Port Cardiol. 2016;35:5–13.
2. Araújo Gonçalves P, Ferreira J, Aguiar C, et al. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J. 2005;26:865–72.
3. Steyerberg EW, Eijkemans MJ, Harrell FE Jr, et al. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. Med Decis Making. 2001;21:45–56.
4. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the Prospective Cardiovascular Munster (PROCAM) study. Circulation. 2002;105:310–5.
5. 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;24:987–1003.
6. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ. 2007;335:136–47.
7. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008;336:1475–82.
8. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds risk score. JAMA. 2007;297:611–9.
9. Ridker PM, Paynter NP, Rifai N, et al. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds risk score for men. Circulation. 2008;118:2243–51.
10. De Backer G, Ambrosionie E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts). Eur Heart J. 2003;24:1601–10.
11. Vikhireva O, Pajak A, Broda G, et al. SCORE performance in Central and Eastern Europe and former Soviet Union: MONICA and HAPIEE results. Eur Heart J. 2014;35:571–7.
12. Mortensen MB, Afzal S, Nordestgaard BG, et al. The high-density lipoprotein-adjusted SCORE model worsens SCORE-based risk classification in a contemporary population of 30 824 Europeans: the Copenhagen General Population Study. Eur Heart J. 2015;36:2446–53.
13. Cooney MT, Dudina AL, Graham IM, for the SCORE investigators. SCORE ELD – Extending risk estimation to older people. Eur Heart J. 2009;29 Suppl:266–77.
14. Graham IM, Cooney MT. Risks in estimating risk. Eur Heart J. 2014;35:537–9.
15. Perk J, de Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33:1635–701.
16. Cooney MT, Selmer R, Lindman A, et al. Cardiovascular risk estimation in older persons: SCORE O.P. Eur J Prev Cardiol. 2015. Jun 3. pii: 2047487315588390.
17. Antman EM, Cohen M, Bernink PJLM, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000;284:835–42.
18. Boersma E, Pieper KS, Steyerberg EW, et al., for the PURSUIT Investigators. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. Circulation. 2000;101:2557–67.
19. Granger CB, Goldberg RJ, Dabbous OH, et al., for the Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163:2345–53.
20. Aragam KG, Tamhane UU, Kline-Rogers E, et al. Does simplicity compromise accuracy in ACS risk prediction? A retrospective analysis of the TIMI and GRACE risk scores. PLoS One. 2009;4:e7947, http://dx.doi.org/10.1371/journal.pone.0007947.
21. Fox KA, Fitzgerald G, Puymirat E, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. BMJ Open. 2014;4:e004425.
22. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in

patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2999–3054.
23. Roffi M, Patrono C, Collet J-P, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2015, http://dx.doi.org/10.1093/eurheartj/ehv320.
24. Bakus BE, Six AJ, Kelder JH, et al. Risk scores for patients with chest pain: evaluation in the emergency department. Curr Cardiol Rev. 2011;7:2–8.
25. Fox KA, Anderson FA Jr, Dabbous OH, et al. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). Heart. 2007;93:177–82.
26. Bawamia B, Mehran R, Qiu W, et al. Risk scores in acute coronary syndrome and percutaneous coronary intervention: a review. Am Heart J. 2013;165:441–50.
27. Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. NICE guideline 94 March 2010. http://www.nice.co.uk/guidance/CG94