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Editorial

# Score2: A New Updated Algorithm to Predict Cardiovascular Disease Risk in Europe

The recently published guidelines of the European Society of Cardiology for the prevention of cardiovascular diseases presented in August 2021 at the virtual European Society of Cardiology congress recommend the use of the SCORE2 risk index instead of the classic SCORE risk index to calculate the cardiovascular risk (specifically, ten-year fatal and nonfatal risk) in a healthy population under the age of 70 years, with a level of evidence IB. This new risk index was developed with the collaboration of about 200 investigators, including 45 cohorts in 13 countries with 700,000 participants, and covers the known risk factors for heart and circulatory diseases such as age, sex, lipid levels, blood pressure, and smoking. In addition, it divides the countries into four groups of risk and uses a competing risk model, adjusting the risk for the probability of having another event, which enables better estimation of the risk of fatal and nonfatal events in a younger population (40-69 years).


CARDIOVASCULAR DISEASES (CVDs) remain a major cause of morbidity and mortality in Europe, and were responsible for an estimated 18.6 million deaths in 2019.[1] The European Society of Cardiology (ESC) advocates the use of risk-prediction models to enhance healthcare and population-wide prevention.[2] In theory, the goal is to identify people at higher risk of CVD who could benefit most from preventive action.[3]

The Systematic Coronary Risk Evaluation (SCORE)[4] that combined results from 12 European cohort studies, 250,000 patient-data sets, three million person-years of observation, and 7,000 fatal CV events, was the first calculator model used by the ESC to prevent CVD events[5] and, as recently as 2021, was recommended by all ESC prevention guidelines.

## The Systematic Coronary Risk Evaluation: Not Perfect and Outdated

However, SCORE has some major limitations, which are listed as follows[4]:

- It includes only fatal CVD ten-year outcomes, meaning it underestimates total CVD burden, which in recent decades has shifted toward nonfatal outcomes, especially for younger people.
- SCORE does not allow for variations of risk across countries from the same risk region, meaning it may underestimate risk in these circumstances.
- SCORE was developed from cohorts recruited before 1986 and has not been systematically "recalibrated" (statistically adapted) to contemporary CVD rates, meaning it is not ideal for use in contemporary European populations.

To address these limitations emerged the ESC Cardiovascular Risk Collaboration, situated in the ESC's European Heart Health Institute in Brussels, a collaboration of academics, policy makers, and end-users that was established by the ESC in 2019 to help develop improved tools for predicting European CVD risk. This resulted in the newly updated tool, the SCORE2.[3] The SCORE2 working group and the ESC Cardiovascular risk collaboration group provided the development, validation, and illustration of SCORE2 to estimate ten-year fatal and nonfatal CVD risk in individuals in Europe without previous CVD or diabetes aged 40-to-69 years.[3]

## Development of the New SCORE2 Model

The SCORE2 risk index was developed with the collaboration of about 200 investigators. This remarkable task involved multiple consecutive steps (see Fig 1). First, to enable reliable estimation of age and sex-specific relative risks, the SCORE2 working group derived prediction models for fatal and nonfatal CVD outcomes using individual participant data from 45 prospective cohorts involving 677,684 participants in 13 countries.[6] Second, to adapt risk prediction models to the circumstances of each European region, the working group had to recalibrate the derived risk models using estimated contemporary age and sex-specific incidences and risk factor distributions.[7] Third, to enhance

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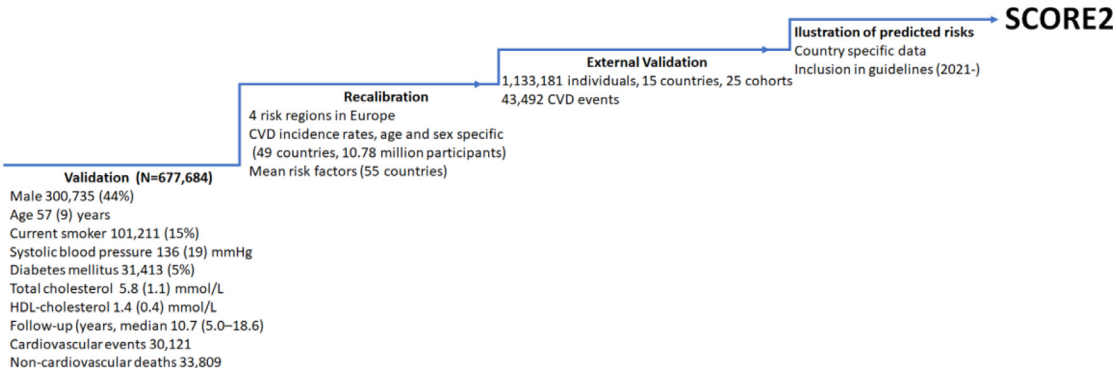


Fig 1. SCORE2 development.

validity and generalizability, external validation was completed using individual participant data from a further 25 prospective cohorts involving 1,133,181 individuals in 15 European countries.[4] In addition, to illustrate the variation of CVD risk across European regions, they applied advanced modeling to contemporary populations.[1,4,5,8]

For the development of the new model, individual participant data were used from 44 cohorts included in two of the largest cohorts in Europe and the United Kingdom, the Emerging Risk Factor Collaboration (ERFC)[9,10] and the UK Biobank.[11] The Emerging Risk Factor Collaboration has collated and unified individual participant data from many long-term prospective cohort studies of CVD risk factors and outcomes. The UK Biobank is a single large prospective cohort study with individual participant data on approximately 500,000 participants with an age of 40 years or more, recruited across 23 UK-based assessment centers during 2006 to 2010,[9,12] and followed-up for cause-specific morbidity and mortality through linkages to routinely available national datasets and disease-specific registers. For recalibration purposes, the SCORE2 working group obtained country-specific CVD mortality rates reported by the World Health Organization and estimated fatal and nonfatal CVD incidences.[13] The incidence rates predicted by the recalibrated models for low- and moderate-risk regions were compared with 2018 incidence rates as reported in national registry data from the Netherlands, Denmark, United Kingdom, Germany, and Spain.[1] For regions with high and very high risk, the SCORE2 working group used multipliers derived from Clinical Practice Research Datalink,[9] the Finnish CVD register,[14] the Swedish population data (linked to the Swedish National Inpatient and cause of death registries), the Estonian Biobank, and the Health, Alcohol, and Psychosocial factors In Eastern Europe study.[10]

The primary outcome was CVD defined as a composite of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. The CVD mortality component of the primary outcomes corresponds to the endpoint definition of the original SCORE model and includes death due to coronary heart disease, heart failure, stroke, and sudden death.[1] Follow-up was until the first nonfatal myocardial infarction, nonfatal stroke, death, or end of the registration period.[3]

## Updated Methods and Data: Statistical Analysis and Data Source

The statistical analysis was conducted using Fine and Gray competing risk-adjusted models stratified by cohort,[15] and in the sex-specific models included the following predictors: age, current smoking, history of diabetes mellitus, systolic blood pressure, and total and HDL cholesterol. The risk factors were selected due to their predictive ability, as well as their availability in derivation cohorts, target populations for screening, and population statistics needed for model recalibration.[15] Importantly, it should be mentioned that previous research showed that associations of these risk factors with CVD declined with increasing age. Thus, age interactions were added for all predictors. To maximize statistical power when estimating age interactions, risk models were derived in participants aged 40-to-79 years at baseline without previous CVD. However, SCORE2 risk models are intended for use in people aged 40-to-69 years. In a parallel initiative, a risk score for individuals older than 70, SCORE2-OP, has been developed and also recently published using similar methods assessing participants aged 70-to-89.[16]

## More Granularity: Four Regions According to Cardiovascular Risk

The further recalibration for four different regions in Europe is a new aspect, with the continent divided into low-, medium-, high-, and very high-risk areas according to their most recently reported World Health Organization age and sex-standardized overall CVD mortality rates per 100,000 population. The four groupings were low risk (<CVD per 100,000 such as Spain, France, the United Kingdom, and Denmark), moderate risk (100-150 CVD per 100,000), high risk (150-300 CVD per 100,000), and very high risk (>300 CVD per 100,000, which include the Russian Federation, eastern European, and some North African countries).[3]

## Advantages of SCORE2 over SCORE

SCORE2 was designed to enhance the identification of individuals at higher risk of developing CVD across Europe. In

comparison with the SCORE model, SCORE 2 has the following advantages[1,2]:

- Much larger derivation and validation cohorts.
- SCORE2 provides risk estimates for the combined outcome of fatal and nonfatal CVD events, in contrast with SCORE's use of only CVD mortality. Furthermore, SCORE2 has been systematically recalibrated, using the most contemporary and representative CVD rates available, whereas the original SCORE model was based on data collected before 1986.
- SCORE2 accounts for the impact of competing risks from non-CVD deaths, whereas SCORE did not do so. This statistical adjustment prevents overestimation of CVD risk and overestimation of the benefit of treatment in populations in whom the risk of competing non-CVD deaths is high.
- The recalibration of SCORE2 to four distinct European regions defined by varying CVD risk levels improves on the 2-level regional stratification provided by SCORE. Furthermore, as the recalibration used for SCORE2 avoids reliance on sparse cohort or country-level data, it provides recalibrated calculators tailored to sex-specific CVD rates and risk factor levels of each region (potential for country-specific charts).
- SCORE2 improved overall risk discrimination (difference in C-index: 0.0100, 95% confidence interval [CI] 0.0085-0.0115; $p < 0.001$), particularly at younger ages (difference in C-index at ages 40-50 years: 0.0213, 95% CI 0.0162-0.0265; $p < 0.001$) and for nonfatal CVD outcomes (difference in C-index: 0.0113, 95% CI 0.0097- 0.0130; $p < 0.001$).
- Recalibration methods can be, when needed, readily applied to provide country-specific regular updates with changing CVD in the future.

## Limitations of SCORE2

So, is this the definitive CVD risk tool? Despite substantive improvements it hardly would be definitive. There are some potential limitations that must be taken in consideration; for example, the authors derived risk prediction models from 45 cohorts, mostly in European regions and populations at low- or moderate-risk CVD risk. Ideally, however, the derivation of risk models for use in high- and very high-risk countries would have involved large, nationally representative, prospective cohorts in these countries, coupled with prolonged follow-up and validation of fatal and nonfatal CVD endpoints. Unfortunately, generaly, such data do not yet exist. Indeed, even in low- and moderate-risk regions, the cohorts involved may not be nationally representative, reflecting past periods of time or self-selected participants such as healthy volunteers. Although healthy volunteer bias can lead to low estimates of absolute risk, relative risks generally are unaffected. Furthermore, this approach assumes that the relative risks obtained in the derivation dataset are transferable across different populations, as evidenced by broadly similar relative risk and good discrimination in external validation populations in all regions. The authors recalibrated models using nationally representative incidence rates from all regions, an important step not commonly considered by other CVD risk scores, avoiding the limitations of miscalibration provided by potentially nonrepresentative incidence rates in cohort studies. Data on medication use, family history, socioeconomic status, nutrition, physical activity, renal function, or ethnicity were not available in cohorts and registries used for model derivation and recalibration. Hence, interpretation of SCORE2 estimates may require clinical judgment, especially for individuals in whom these factors may be relevant (those taking lipid or blood pressure lowering treatments, family history of CVD, chronic kidney disease, or in at-risk socioeconomic and ethnic groups). And finally, this risk model might have underestimated CVD risk because data used to estimate multipliers were likely to include some people already on CVD prevention therapies (eg, statins or antihypertensive medication), but available data were insufficient to evaluate this possibility.

## Conclusions

The new SCORE2 and SCORE2-OP in the >70-years old population are updated algorithms tailored to European populations to predict ten-year risk of first-onset CVD that will enhance the identification of individuals at higher risk of developing CVD across Europe. Developed with state-of-the-art methodology, in conjunction with larger derivation and validation cohorts, they present a better ability to discriminate cardiovascular risk compared with the previous guideline recommended SCORE. Both have been added to the 2021 ESC guidelines on cardiovascular disease prevention guidelines, replacing the SCORE as a risk calculator, with a high level of evidence and recommendation (IB).[17]

## Conflict of Interest

The authors have no conflict of interest or financial involvement with this manuscript.

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