

Original Research

Validation of the HellenicSCORE (a Calibration of the ESC SCORE Project) Regarding 10-Year Risk of Fatal Cardiovascular Disease in Greece

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Introduction: There is increasing interest in indexes that estimate the individual risk of developing a cardiovascular disease (CVD) event; the European Society of Cardiology (ESC), in the latest guidelines (2012) for CVD prevention, acknowledged the importance of risk evaluation through risk scores, i.e. the ESC SCORE (Systematic COronary Risk Estimation). However, there has been much discussion about the reliability of such CVD risk scores among different populations. The ESC SCORE is a CVD risk-specific tool for Europe, based on datasets from 12 European countries (Greece did not participate). In the mid-2000s the HellenicSCORE, a calibration of the ESC SCORE based on national mortality data and prevalence regarding risk factors as reported by the ATTICA study, was proposed for the Greek population and became a part of daily clinical practice. This validation of the HellenicSCORE was performed using the 10-year follow-up examination of the ATTICA study participants.

Methods: Of the 3042 participants of the ATTICA study (enrolment 2001-2002), 2583 were contacted in the 10-year follow-up (2011-2012). The HellenicSCORE as calculated using participants' baseline characteristics was tested against the 10-year CVD event rates.

Results: The 10-year fatal or non-fatal CVD incidence rate was 15.7% (19.7% in men and 11.7% in women). The HellenicSCORE correctly predicted 95.6% of fatal CVD cases and 93.2% of the fatal and non-fatal CVD cases. No interactions with sex, age group or comorbidities were observed.

Conclusion: The HellenicSCORE is a valid tool for CVD risk estimation in Greek subjects. The present work suggests a calibration methodology that could be used by other nations for CVD risk estimation.

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The prediction of future cardiovascular disease (CVD) events has received increasing attention in recent years. Identifying individuals who are vulnerable to developing a fatal or non-fatal CVD event is a main target of the vast majority of prevention programs, since it allows better management, facilitates preventive efforts, and can therefore delay or, even better, prevent the occurrence of an adverse outcome. The most recent (2012) guidelines of the Europe-

an Society of Cardiology (ESC) strongly recommended that CVD risk prediction should be a common procedure before starting any treatment or therapy.¹ The challenge of correctly classifying individuals at high risk is also a cornerstone of risk prediction modeling, since the up-to-date models have been criticised for serious misclassification problems, especially when applied to other populations than those they were created for.² One of the best-known CVD risk models is the Framing-

ham Heart Study sheets; since the early 1990s many physicians and public health policy makers have used this risk model in clinical practice, as well as in strategic planning and research.³ The Framingham Heart Study risk sheet provides estimates of developing angina pectoris, or myocardial infarction, or coronary heart disease death, over the course of 10 years, for persons without known heart disease. However, several investigators have advocated that risk prediction models have so far not been very successful, since substantial misclassification occurred when the Framingham Heart Study Sheets were applied to other populations, especially non-Caucasian, although the set of CVD risk factors was consistent between studies.⁴⁻⁷

More recently, in 2003, the Working Group on Epidemiology and Prevention of the European Society of Cardiology (ESC) proposed a risk prediction chart based on data from 12 European cohort studies, which included 205,000 persons and 2.7 million years of follow-up, where 5652 fatal coronary heart disease events were observed: the SCORE (Systematic COronary Risk Estimation) project.⁸ The separation of European countries into “high” and “low” risk was an innovation of these risk charts; however, the inclusion of only 12 cohorts raised several concerns about the applicability of the charts for estimating risk in all European populations. In 2007, a group of scientists presented a calibration of the ESC SCORE, the HellenicSCORE,^{9,10} which is a statistical model that predicts the 10-year risk for fatal CVD events based on the actual sex, age, smoking habits, total cholesterol and systolic blood pressure levels of the Greek population and using the risk point-estimates suggested by the ESC SCORE model. However, because of the lack of relevant follow-up studies in the Greek population, this calibration suffered from a serious methodological drawback, since no actual CVD events were used.^{9,11} Moreover, the calibration methodology presumed that the national statistics for CVD mortality and the prevalence of risk factors are unchanged over time. Thus, it is a matter of emerging importance to validate the risk tool and the applied methodology, taking into account potential changes over time.

Therefore, and based on the 10-year follow-up of the ATTICA Study,¹² the aim of this work was to calculate an up-to-date CVD risk model for the Greek population, based on the concept of the ESC SCORE charts, to validate the HellenicSCORE charts and to propose a methodological framework that other European populations can use to develop their own risk charts based on ESC SCORE.

Methods

The original HellenicSCORE charts

The HellenicSCORE charts were developed in accordance with the ESC SCORE. In particular, a recalibration method was proposed, based on the Greek risk factor prevalence that was obtained from the baseline evaluation of the ATTICA study in 2001-2002,^{9,12} as well as the annual death rates obtained from the World Health Organization (WHO) mortality database for 2002,¹³ in accordance with the rules of the International Classification of Diseases.⁹ The recalibration method used was the one recommended by D’Agostino et al,¹⁴ and was performed separately for men and women.

Briefly, the recalibration method was based on the following steps: first, the average age- and sex-specific levels of systolic blood pressure, total cholesterol and smoking prevalence were predicted, using data from the ATTICA study. Risk factor levels were modelled as quadratic functions of age. Then, using the WHO mortality data, the average annual CVD mortality was calculated for 5-year age-groups. Annual rates were modelled using an age-specific Poisson model, with age included as a piecewise function that joined the mid-points of each age-interval. Annual rates were extrapolated to estimate the cumulative 10-year CVD mortality. The hazard ratios that were based on an analysis of the entire ESC SCORE database, as well those based only on the low CVD risk cohorts (i.e. Spain, Italy and Belgium), were applied. The assumption was that the risk estimates were the same in all countries, although underlying rates may vary. The estimated hazard ratios have been presented elsewhere.⁹

Theory

Validation of the HellenicSCORE

As already mentioned, the HellenicSCORE was based on national mortality data and not on the actual CVD events of the ATTICA study participants. During 2011-2012, the ATTICA study’s investigators performed the 10-year follow up (median follow-up time 8.41 years). Of the 3042 participants initially enrolled in the baseline examination, 2583 were evaluated during the follow up (85% participation rate). No differences were reported regarding the distribution of sex (men 50% vs. 49%, $p=0.613$), obesity (19% vs. 16%, $p=0.208$), anxiety ($p=0.083$), or depression lev-

els ($p=0.173$) between the participants who were followed up and those who were lost to follow up. In brief, the sampling procedure of the follow up was as follows: all 3042 participants were contacted by phone and their vital status was checked. Afterwards, the investigators met the survivors and performed a detailed clinical evaluation. In particular, for the present study, information about participants' vital status (death from any cause or due to CVD) and development of CHD was recorded.

In order to validate the HellenicSCORE, the following procedures were applied. Ten-year fatal and non-fatal CVD events were classified by the participants' age group (i.e. <35 years, 35-45 years, 45-55 years, 55-65 years, 65-75 years, and >75 years) and sex. The 10-year risk for CVD fatal events estimated by the HellenicSCORE was compared with the actual predicted probabilities of CVD deaths through the applied survival model (see statistical analysis), by age group, sex, and classes of total cholesterol and blood pressure levels, as originally described for the ESC SCORE.⁸ The validation analysis was based on smoking status, normal weight (i.e. body mass index, $BMI < 25 \text{ kg/m}^2$) versus overweight ($BMI 25-29.9 \text{ kg/m}^2$) or obesity ($BMI \geq 30 \text{ kg/m}^2$), history of hypercholesterolaemia, as well as hypertension and diabetes at baseline evaluation. Kendall's tau correlation coefficient, a standard method for associating two procedures measuring the same quantity (i.e. the 10-year risk of a fatal event estimated through the HellenicSCORE and the observed risk from the follow-up examination), was used. Moreover, and in order to test whether the HellenicSCORE would be able to predict the risk of future non-fatal CVD events (since the original score was developed for prediction of fatal events) the aforementioned procedure was repeated using the combined 10-year fatal or non-fatal CVD events as outcome. In addition, the classification of subjects (i.e. low-CVD risk vs. high-CVD risk) according to the HellenicSCORE estimation was tested by validation based on the subjects' true CVD outcomes; the classification bias was measured and presented in this work.

Descriptive statistical analysis

Crude, non-fatal and fatal incidence rates of combined CVD (i.e. CHD or stroke) were calculated as the ratio of new cases to the number of people participating in the follow up. Quantitative characteristics of the participants were presented as mean values \pm

standard deviation and qualitative characteristics as frequencies. The hazard ratios of developing a fatal or a non-fatal CVD event during the 10-year period, according to participants' age, sex, cholesterol and systolic blood pressure levels, were estimated using Cox proportional-hazards models. The proportionality of hazards was checked graphically and there was no evidence for non-proportional hazards. Only the aforementioned characteristics were used, so that the estimated model would be in alignment with the already developed HellenicSCORE, thus allowing the risk estimates to be comparable. The time to CVD event was recorded on an annual basis and the actual time of death was used for the analyses. SPSS version 19 (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL, U.S.A.) software was used for all the statistical calculations. The study was approved by the Medical Research Ethics Committee of the supervising institution and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Results

Ten-year cardiovascular disease incidence

The overall 10-year incidence of fatal or non-fatal CVD was 15.7% ($n=317$); 19.7% ($n=198$) for men and 11.7% ($n=119$) for women. Of the 317 CVD events, 46 were fatal (34 men); thus, the overall 10-year fatal CVD rate was 1.8% (3.4% for men and 1.2% for women). Based on the observed person-years, the annual incidence of CVD was 182 new cases per 10,000 men and 110 new cases per 10,000 women participants. The age-sex specific 10-year fatal and non-fatal CVD events are presented in Table 1. The CVD mortality rate among men was almost 3 times greater than that among women (3.34% vs. 1.2%). As regards the non-fatal CVD events, men had an almost twofold greater 10-year incidence than women (16.19% vs. 9.83%). No fatal CVD events were reported for women aged under 45 years, whereas 4 fatal CVD events were observed for men aged under 35 years. For subjects aged over 55 years old, men and women tended to have equal non-fatal CVD incidence, but men suffered more fatal CVD events than women for the same age group.

The baseline values of participants' characteristics that were used for the development of the HellenicSCORE are presented in Table 2. Of the 46 subjects who died from CVD within 10 years, 44 of them

Table 1. Ten-year incidence of fatal and non-fatal cardiovascular disease in men and women who participated in the follow-up evaluation of the ATTICA study.

Age at baseline (years)	Men (n=1013)		Women (n=996)	
	Fatal events	Non-fatal events	Fatal events	Non-fatal events
<35	0.4 (4)	1.0 (10)	0 (0)	0.5 (5)
35-45	0 (0)	1.78 (18)	0 (0)	0.8 (8)
45-55	0.4 (4)	5.04 (51)	0.1 (1)	2.41 (24)
55-65	0.98 (10)	4.34 (44)	0.1 (1)	3.31 (33)
65-75	0.78 (8)	2.47 (25)	0.5 (5)	2.71 (27)
>75	0.78 (8)	1.56 (16)	0.5 (5)	1.0 (10)
Total	3.34 (34)	16.19 (164)	1.2 (12)	9.83 (107)

Data are expressed as % (n).

Table 2. Baseline risk factor levels used to develop the charts, based on the ATTICA study evaluation during 2001-2002.

	Age (years)	Systolic blood pressure (mmHg)	Total cholesterol (mg/dL)	Smoking (%)
Men	>75 (n=42)	138 (19)	197 (35)	7
	65-75 (n=97)	136 (19)	207 (41)	29
	55-65 (n=231)	134 (18)	205 (44)	41
	45-55 (n=434)	128 (16)	204 (39)	50
	35-45 (n=387)	121 (15)	196 (39)	55
	<35 (n=323)	119 (14)	174 (41)	49
Women	>75 (n=37)	146 (18)	218 (37)	5
	65-75 (n=126)	135 (19)	216 (36)	21
	55-65 (n=208)	133 (20)	211 (39)	34
	45-55 (n=376)	121 (18)	206 (40)	42
	35-45 (n=398)	113 (14)	183 (35)	46
	<35 (n=383)	107 (13)	166 (34)	43

Data are expressed as mean (standard deviation) or relative frequencies.

were correctly classified by the HellenicSCORE as having moderate-to-high risk for fatal CVD (i.e. estimated risk >10%), taking into account their baseline characteristics, and only 2 (1 male and 1 female) of the 46 cases with fatal CVD events were classified as low CVD risk (4.4% misclassification of cases). Only 18 of the 317 fatal CVD events (7 males and 11 females) were classified by the HellenicSCORE as having low CVD risk (5.7% misclassification of cases).

To evaluate the accuracy of the HellenicSCORE in predicting future CVD events, the baseline values of the score were classified into the following classes, according to the ESC instructions: <1%, 2-4%, 5-9%, 10-15%, and ≥15%. In Table 3 the number of participants that developed a CVD event is presented according to the aforementioned risk categories. The probabilities of a fatal CVD event that were estimated using the baseline characteristics and the HellenicSCORE were very similar to the predicted prob-

abilities using the observed data from the 10-year follow up. The classification bias of the HellenicSCORE was 4.4% for classifying the observed CVD cases as high CVD risk. Two of the 46 fatal CVD events were incorrectly classified, one male and one female. The misclassification of cases as regards the fatal and non-fatal CVD events was 6.8% (22 out of the 317 events).

The validation was also applied based on smoking status, normal weight (i.e. body mass index, BMI <25 kg/m²) versus overweight (BMI 25-29.9 kg/m²) or obesity (BMI ≥30 kg/m²), history of hypercholesterolaemia, as well as hypertension and diabetes at baseline evaluation. The HellenicSCORE was found to be in line with the actual risk estimates from the fatal CVD risk model, adjusted for the same set of factors included in the HellenicSCORE, for both sexes (men Kendall's tau=0.910, women Kendall's tau=0.894), smokers (Kendall's tau=0.666) and non-smokers (Ken-

Table 3. Ten-year (2001-2011) fatal and non-fatal incidence of cardiovascular disease in men and women who participated in the ATTICA study, according to the HellenicSCORE classification.

HellenicSCORE at baseline examination (2001-2002)	Men (n=1013)		Women (n=996)	
	Fatal events	Non-fatal events	Fatal events	Non-fatal events
≤1%	0.7 (6)	8.9 (59)	0 (0)	2.4 (12)
2-4%	3.1 (7)	22.9 (40)	0.3 (1)	9.0 (25)
5-9%	5.4 (8)	19.3 (36)	1.7 (5)	27.5 (55)
10-14%	6.5 (3)	33.3 (11)	12.2 (6)	39.5 (15)
≥15%	22.2 (10)	45.0 (18)	-	-

Data are expressed as % (n). Note: the HellenicSCORE was developed to predict only fatal cardiovascular events; the presentation of non-fatal events in comparison with the score categories was made in order to test whether the HellenicSCORE was also associated with non-fatal cardiovascular events.

dall's tau=0.722), hypercholesterolaemic (Kendall's tau=0.611) and non-hypercholesterolaemic subjects (Kendall's tau=0.703), diabetic (Kendall's tau=0.668) and non-diabetic subjects (Kendall's tau=0.697), hypertensive (Kendall's tau=0.714) and normotensive subjects (Kendall's tau=0.688), as well as underweight (Kendall's tau=0.6610), normal-weight (Kendall's tau=0.733), overweight (Kendall's tau=0.701) and obese individuals (Kendall's tau=0.634) (all $p < 0.001$).

Discussion

In this study, the validation of the HellenicSCORE was performed using the observed 10-year CVD outcomes of the ATTICA study participants. A higher incidence of fatal CVD outcomes was observed among men as compared with women, while fatal CVD outcomes under the age of 35 occurred only in men. The incidence of non-fatal CVD outcomes was almost twofold higher among men than among women, but only for subjects aged less than 55 years. As regards the validity of the HellenicSCORE, it was revealed that the tool was very accurate for identifying individuals at high risk of a fatal CVD outcome within the decade, but also for identifying individuals at high risk even for a non-fatal CVD event. The accuracy of the estimation was robust for both genders and for various sub-groups of the study sample.

Risk prediction scores have become useful tools at an individual level in daily clinical practice, as well as for the development of future public health strategies to address the burden of CVD. Their use has also been suggested for all individuals, regardless of their medical history, in order to better identify individuals at high risk in the field of CVD pri-

mary prevention,¹⁵ and it is strongly believed that knowledge of the individual CVD risk could motivate subjects to manage their CVD risk factors and thus reduce the burden of the disease.¹⁶ It is a fact that accuracy is a cornerstone of any risk prediction score, so the wide use of risk charts like the Framingham sheets or SCORE, in populations with divergent ethnic, genetic, social and cultural characteristics, and hence variable risk factors, could lead to substantial variability in the prediction of cardiovascular events. It has already been reported that the Framingham Heart Study score sheets or the predictive risk models from northern European countries overestimate the risk in several southern European populations.^{4,6} It is interesting that these differences in the absolute risk were not attributed to the differences in the incidence of the various manifestations of CVD (i.e. fatal, myocardial infarction, and unstable angina). Some investigators have suggested that the inaccuracy of risk prediction could be attributed to the differences in the incidence of CVD between populations.⁵ In particular, the link between hazard ratios derived from Cox proportional-hazards models and the estimation of absolute risk is dependent on some form of "reference" level of risk (i.e. average CVD-free survival of the population from which the model was derived). Thus, if this average survival varies between populations, then the prediction of absolute risk will also vary. In order to resolve this problem for the Greek population, the SCORE models were recalibrated using advanced techniques and the HellenicSCORE was used for CVD primary prevention in Greece.⁹

In this study, the HellenicSCORE proved to be very accurate in predicting both fatal and non-fatal 10-year CVD risk. This should be attributed to the advanced design of the recalibration methodology

that was used in the first place,⁹ which took into account the mortality data from the National Statistical Services and prevalence data regarding smoking, total cholesterol and blood pressure levels, as reported by the ATTICA epidemiological study. The validation was performed using the 10-year follow-up examination of the subjects in the ATTICA study, which is the only epidemiological study in Greece with a long follow-up time that could be comparable to the estimated 10-year CVD risk estimated by other scores. Thus, the HellenicSCORE is a valid tool that can be used for the accurate CVD risk estimation of Greek individuals, who are recently facing an increasing risk of CVD.¹⁷ Recently, investigators from Italy reported that the Italian score was also accurate and could thus be used to estimate the 10-year CVD risk among Italian people.¹⁸

The accuracy and the validity of the CVD risk estimation models represents an important topic in the field of CVD prevention, because the identification of subjects at high risk of CVD is the first step towards reducing the burden of the disease.¹⁹ Several biomarkers, techniques and lifestyle characteristics are under investigation regarding their role in improving the predictive accuracy as well as the cost-effectiveness of existing scores.²⁰⁻²²

Limitations

The strength of the present work is that a middle-aged population was studied for developing CVD, which is very important when addressing pathobiological research hypotheses concerning CVD prevention. However, the assessment of various clinical risk factors or the levels of biological factors was performed only once, at baseline, and therefore their effect on CVD risk may have been over- or underestimated. Nevertheless, the applied methodology is comparable to that of other prospective epidemiological studies in Europe and the US. The sample used for the validation procedure (i.e. the ATTICA study's database) may not be representative of the whole Greek population. Moreover, there is a lack of prospective studies that have performed a 10-year follow up in order to validate the CVD risk estimation models for the entire Greek population. However, it should be underlined that roughly half of the population lives in the surveyed area. The impact of other risk factors modulating disease risk, such as diet and psychological factors, also needs to

be considered, but the aim of the present work was to validate the tool.

Conclusions

Estimation of the risk of future CVD events through easily applicable scores is an attractive and dynamic field in public health research, as well as in primary prevention, since it has the potential to stimulate more effective preventive strategies. This study found that the HellenicSCORE, a calibration of the ESC SCORE for the Greek population, was an accurate tool, with a very low classification bias. Thus, its use in daily practice may accurately estimate an individual's risk of suffering a future CVD event and could be a reason for the individual to initiate various changes in behavior, with a view to achieving a new healthier lifestyle. Clinicians, healthcare practitioners, and public health policy makers may use this tool for better prevention of the CVD epidemic in the future.

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