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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

Martin B. Mortensen[1], Shoaib Afzal[2,3], Børge G. Nordestgaard[2,3]*, and Erling Falk[1]

[1]Atherosclerosis Research Unit, Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [2]The Department of Clinical Biochemistry and The Copenhagen General Population Study, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark; and [3]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

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Aims Recent European guidelines recommend to include high-density lipoprotein (HDL) cholesterol in risk assessment for primary prevention of cardiovascular disease (CVD), using a SCORE-based risk model (SCORE-HDL). We compared the predictive performance of SCORE-HDL with SCORE in an independent, contemporary, 'low-risk' European population, focusing on ability to identify those in need of intensified CVD prevention.

Methods and results Between 2003 and 2008, 46 092 individuals without CVD, diabetes, or statin use were enrolled in the Copenhagen General Population Study (CGPS). During a mean of 6.8 years of follow-up, 339 individuals died of CVD. In the SCORE target population (age 40–65; $n = 30\,824$), fewer individuals were at baseline categorized as high risk (≥5% 10-year risk of fatal CVD) using SCORE-HDL compared with SCORE (10 vs. 17% in men, 1 vs. 3% in women). SCORE-HDL did not improve discrimination of future fatal CVD, compared with SCORE, but decreased the detection rate (sensitivity) of the 5% high-risk threshold from 42 to 26%, yielding a negative net reclassification index (NRI) of −12%. Importantly, using SCORE-HDL, the sensitivity was zero among women. Both SCORE and SCORE-HDL overestimated risk of fatal CVD. In well-calibrated models developed from the CGPS, HDL did not improve discrimination or NRI. Lowering the decision threshold from 5 to 1% led to progressive gain in NRI for both CVD mortality and morbidity.

Conclusion SCORE-HDL did not improve discrimination compared with SCORE, but deteriorated risk classification based on NRI. Future guidelines should consider lower decision thresholds and prioritize CVD morbidity and people above age 65.

Keywords SCORE • HDL • risk assessment • Copenhagen General Population Study

Introduction

Cardiovascular disease (CVD) remains a leading cause of mortality, morbidity, and healthcare costs in Europe.[1] The most recent European guidelines for the management of dyslipidaemias[2] and prevention of CVD[3] recommend including high-density lipoprotein (HDL) cholesterol in risk assessment for the primary prevention of CVD. For this purpose, the guidelines provide a new SCORE (Systematic COronary Risk Evaluation)-based model that incorporates HDL cholesterol as an independent predictor (SCORE-HDL), and this model received a Class I recommendation.[2]

However, to date, the new SCORE-HDL risk model has not been tested head-to-head against the original SCORE model, nor has it been validated in an independent cohort. In the present study, we compared the clinical performance of these two risk assessment models and evaluated the incremental predictive value of HDL cholesterol in an independent and contemporary European population, the Copenhagen General Population Study (CGPS).

* Corresponding author. Tel: +45 3868 3297, Email: boerge.nordestgaard@regionh.dk

Methods

Copenhagen General Population Study

The CGPS is an ongoing prospective cohort study of the Danish general population.[4–6] It began enrollment of participants in 2003, and participants were randomly selected through the Danish Civil Registration system to reflect the Danish population aged 20–100. All participants are white and of Danish descent. For this study, we included participants enrolled from 2003 through 2008; for trend of risk factors and preventive medications over time, we additionally included participants through 2012. After exclusion of individuals with diabetes, pre-existing CVD, on statin therapy, or with missing information at baseline examination, 46 092 individuals from 2003–08 were available for this study. The study was conducted in accordance with the Declaration of Helsinki and approved by Herlev Hospital and a Danish ethical committee. Written informed consent was obtained from all participants.

Baseline examination and cardiovascular disease endpoints

The CGPS baseline examination included a questionnaire, physical examination, and blood sampling for biochemical measurements. Blood pressure was measured using an automated Digital Blood Pressure Monitor (Kivex) after 5 min of rest with the individual in the sitting position. Total and direct HDL cholesterol were measured using colorimetric assays (Boehringer Mannheim, Mannheim, Germany; Konelab, Thermo Fisher Scientific, Waltham, MA, USA).

In agreement with the definitions used in the SCORE project, fatal CVD was defined as deaths (underlying cause) from ICD-10 codes I10–25, I44–51, I61–73, and R96,[7] obtained by linkage to the national Danish Cause of Death Registry covering all deaths in Denmark from 1977 through April 2013. In sensitivity analyses, we expanded this definition of fatal CVD. First, all deaths in which the above ICD-10 codes were registered as a contributing cause of death were included (underlying cause + contributing cause). Next, we also included all deaths that occurred within 30 days after a myocardial infarction (MI) or stroke that were identified by linkage to the national Danish Patient Registry covering all Danish hospitals from 1977 through April 2013, but not recorded in the Cause of Death Registry with any of the above ICD-10 codes (underlying cause + contributing cause + 30-day criteria).

For comparison, we also explored an endpoint mainly driven by CVD morbidity, that is fatal CVD + non-fatal MI or stroke. Fatal CVD was defined as in SCORE (underlying cause of death), and the other components of the combined endpoints were identified in the national Danish Cause of Death and Patient Registries, essentially as done previously;[4,6,8] stroke was ischaemic and haemorrhagic combined. Follow-up was through 10 April 2013.

All individuals in Denmark are assigned a personal identification number at birth or immigration by which they can be traced in the registries, and therefore, follow-up was without losses.

Target population for SCORE

The SCORE and SCORE-HDL models predict fatal CVD in individuals aged 40–65 free of diabetes and CVD.[2,3,7] Thus, when comparing the SCORE-HDL model with the SCORE model, we limited the study population to those who underwent baseline examination between 40 and 65 years of age ($n = 30\,824$).

SCORE and SCORE-HDL models

The European Society of Cardiology (ESC) introduced the SCORE risk model in 2003,[7,9] including age, sex, smoking status, total cholesterol, and systolic blood pressure. Originally two versions of SCORE were provided, one for countries with a high risk (high incidence) of fatal CVD, the other for low-risk countries.[7] In 2009, two additional versions of SCORE (for high and low risk) were introduced that incorporated HDL cholesterol as an additional independent variable (SCORE-HDL),[10] models that subsequently were recommended in the new guidelines.[2,3] High risk was defined as ≥5% 10-year risk of fatal CVD.[3]

Statistical analysis

The low-risk SCORE and SCORE-HDL models were used to predict risk of fatal CVD, as recommended by the recent ESC guideline.[3] In contrast to the SCORE model,[7] the SCORE-HDL model has not been published but is used to estimate risk on the online risk calculator, HeartScore,[11] and underlies the available risk charts. The SCORE-HDL model was kindly provided on request by Dr Cooney.[10,12]

First, we analysed the association of SCORE risk factors with fatal CVD and fatal CVD + non-fatal MI or stroke in the overall population using Cox regression models analysing time to event. Analyses were multivariable adjusted for age, sex, smoking status, total cholesterol, systolic blood pressure, and HDL cholesterol. Furthermore, we assessed the added discriminative power of HDL cholesterol in the overall cohort by computing Harrel's c-statistics of Cox models with and without HDL cholesterol included.

Second, we examined the calibration of SCORE and SCORE-HDL by calculating the predicted-to-observed (P/O) event ratio and the Hosmer–Lemeshow χ^2 (goodness-of-fit). As the mean follow-up time in the CGPS was 6.8 years, we used the SCORE and SCORE-HDL models to calculate 7-year risk of fatal CVD to assess calibration. This was done by a slight modification of the baseline survival function in these models. When assessing calibration, the observed number of fatal CVD events at 7 years was adjusted for variable follow-up time using the Kaplan–Meier estimate.

Third, we compared the discriminative power of SCORE and SCORE-HDL with Harrell's c-statistics.

We further calculated the binary net reclassification index (NRI) across the 5% high-risk threshold when comparing SCORE-HDL with SCORE for individuals with and without fatal CVD during follow-up.

Finally, to look into the consequences of using lower treatment thresholds, we lowered the cut-point stepwise from 5 to 1% and calculated the associated changes in sensitivity, specificity, and NRI.

Additional information on statistics and methods for creation of SCORE-like risk models from the CGPS are provided in Supplementary material online, *Methods*. Analysis was performed using Stata version 13.1 SE (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics and observed events among the 46 092 participants included in this study are shown in *Table 1*. During a mean of 6.8 years of follow-up, we observed 339 fatal CVD events, 116 (34%) of which were caused by coronary heart disease (CHD). We also observed 1875 fatal CVD + non-fatal MIs or strokes.

Predictors for fatal cardiovascular disease and fatal cardiovascular disease + non-fatal myocardial infarction or stroke in the overall population

Multivariable adjusted hazard ratios for fatal CVD and fatal CVD + non-fatal MI or stroke are shown in *Table 2*. Age, sex, and smoking were associated with both endpoints in the overall population, but total cholesterol, systolic blood pressure, and HDL cholesterol were mainly associated with fatal CVD + non-fatal MI or stroke.

Table 1 Baseline characteristics and observed cardiovascular events in the Copenhagen General Population Study

Characteristics	All		Age 40–65 years	
	Men	Women	Men	Women
Participants, *n*	19 867	26 225	13 337	17 487
Age, median (IQR), year	55 (46–65)	55 (46–65)	53 (47–59)	53 (46–60)
Systolic blood pressure, median (IQR), mmHg	140 (130–155)	135 (120–150)	140 (129–152)	132 (120–148)
Plasma parameters, median (IQR)				
Total cholesterol, mmol/L	5.6 (5.0–6.3)	5.7 (5.0–6.4)	5.7 (5.1–6.4)	5.7 (5.0–6.4)
HDL cholesterol, mmol/L	1.4 (1.1–1.7)	1.8 (1.4–2.1)	1.4 (1.1–1.7)	1.8 (1.4–2.1)
Current smokers, %	24	21	25	23
Antihypertensive medication, %	12	14	9	10
SCORE,[a] median (IQR), % fatal CVD/10 years	—	—	1.9 (0.8–3.9)	0.6 (0.2–1.6)
SCORE-HDL,[a] median (IQR), % fatal CVD/10 years	—	—	1.7 (0.9–3.1)	0.3 (0.1–0.8)
Fatal CVD events, *n*	201	138	45	17
Fatal CVD + non-fatal MI or stroke, *n*	1022	853	451	316

IQR, inter-quartile range; SCORE, Systematic COronary Risk Evaluation; HDL, high-density lipoprotein; CVD, cardiovascular disease; MI, myocardial infarction.
[a]The recommended target population for risk assessment using SCORE is limited to people 40–65 years of age.

Table 2 Independent associations of SCORE risk factors with cardiovascular events in the Copenhagen General Population Study

Risk factor	HR (95% CI) fatal CVD			HR (95% CI) fatal CVD + non-fatal MI or stroke		
	Overall (*n* = 46 092)	Men (*n* = 19 867)	Women (*n* = 26 225)	Overall (*n* = 46 092)	Men (*n* = 19 867)	Women (*n* = 26 225)
Age, per year	1.15 (1.13–1.16)	1.13 (1.12–1.15)	1.16 (1.14–1.19)	1.08 (1.08–1.09)	1.08 (1.07–1.09)	1.08 (1.08–1.09)
Sex	1.91 (1.51–2.41)	—	—	1.52 (1.37–1.68)	—	—
Current smoking	2.20 (1.75–2.77)	2.44 (1.83–3.24)	1.84 (1.24–2.72)	1.85 (1.67–2.05)	1.79 (1.57–2.05)	1.94 (1.66–2.26)
Total cholesterol[a]	1.10 (0.98–1.23)	1.11 (0.95–1.28)	1.05 (0.87–1.26)	1.13 (1.08–1.19)	1.15 (1.08–1.23)	1.09 (1.02–1.18)
Systolic blood pressure[a]	1.04 (0.94–1.16)	0.98 (0.86–1.12)	1.11 (0.94–1.31)	1.18 (1.13–1.23)	1.13 (1.06–1.19)	1.24 (1.15–1.32)
HDL cholesterol[a]	0.88 (0.79–0.99)	0.92 (0.80–1.05)	0.86 (0.73–1.01)	0.87 (0.83–0.91)	0.88 (0.83–0.94)	0.88 (0.82–0.94)

Multivariable adjusted Cox hazard ratios (HR).
SCORE, Systematic COronary Risk Evaluation; HDL, high-density lipoprotein; CVD, cardiovascular disease; MI, myocardial infarction; HR, hazards ratio.
[a]HRs are standardized per unit SD increase in the variable.

Concerning the SCORE-defined endpoint (fatal CVD), adding HDL cholesterol to a Cox regression model including sex, age, smoking, total cholesterol, and systolic blood pressure did not improve discrimination between cases and non-cases assessed by Harrell's c-statistics in the overall population (0.887 vs. 0.888, $P = 0.49$). Use of antihypertensive medication was associated with increased risk of both fatal CVD and fatal CVD + non-fatal MI or stroke (see Supplementary material online, *Table S1*), but did not improve discrimination assessed by Harrell's c-statistics.

Individuals identified by SCORE and SCORE-HDL to be offered intensified prevention

Predicted 10-year fatal CVD risk calculated by SCORE and SCORE-HDL correlated strongly (Spearman's rho 0.93; $P < 0.0001$), but the median predicted risk was lower for SCORE-HDL compared with SCORE for both men and women (*Table 1*). Consequently, fewer people passed the 5% high-risk threshold using SCORE-HDL instead of SCORE (*Figure 1*). With SCORE-HDL, 10% of men and 1% of women were categorized as high risk, compared with 17% of men and 3% of women using SCORE.

Predictive performance of SCORE and SCORE-HDL

To assess calibration of SCORE and SCORE-HDL in the target population (age 40–65), we slightly modified the baseline survival function of these risk algorithms to calculate 7-year risk for fatal CVD. Surprisingly, both models overestimated risk substantially compared with observed events (*Figure 2* and *Table 3*). SCORE overestimated risk by 4.9-fold in men and by 5.5-fold in women.

The SCORE-HDL model did not improve discrimination of fatal CVD compared with SCORE, as evidenced by similar Harrell's c-statistics (*Table 3*). However, the sensitivity of the 5% high-risk threshold decreased from 42 to 26% using SCORE-HDL instead of SCORE, while the specificity increased less, giving rise to a negative NRI. These changes went in the same direction in men and women separately (*Table 3* and see Supplementary material online, *Figure S1*). Thus, replacing SCORE with SCORE-HDL for risk assessment decreased the sensitivity of the high-risk threshold for detecting fatal CVD events by 16% and only increased specificity for detecting non-events by 4%, combined giving rise to a negative NRI of −12%. Importantly, the sensitivity was zero among women with SCORE-HDL.

Next, we assessed the predictive performance of the SCORE and SCORE-HDL models using the combined endpoint of fatal CVD + non-fatal MI or stroke (*Table 4* and see Supplementary material online, *Figure S1*). Although HDL cholesterol was associated with the combined endpoint (*Table 2*), SCORE-HDL did not improve the discriminative performance for this endpoint compared with SCORE (c-statistics 0.714 vs. 0.712, $P = 0.75$). Similar to the results obtained with fatal CVD as endpoint, the sensitivity of the 5% high-risk threshold decreased from 26 to 16% using SCORE-HDL instead of SCORE, resulting in a negative NRI of −5% (*Table 4*). Among women, the sensitivity was 2%.

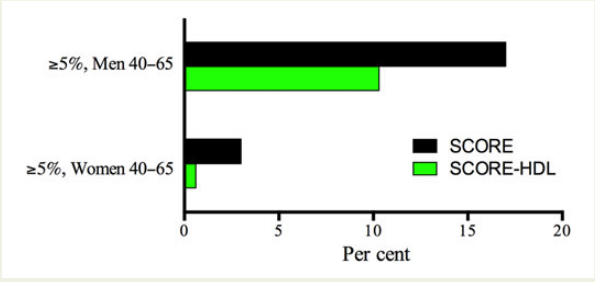

Figure 1 Proportion of individuals in the target population classified as high risk. The percentage of individuals classified as high risk (≥5% 10-year risk of fatal cardiovascular disease) was lower using SCORE-HDL (green) compared with SCORE (black). SCORE, Systematic COronary Risk Evaluation; HDL, high-density lipoprotein.

Risk prediction models derived from the Copenhagen General Population Study cohort (SCORE/CGPS)

To get the most reliable assessment of the incremental predictive value of HDL cholesterol in the CGPS cohort, we developed a SCORE-like risk model from the CGPS based on predictors and outcomes similar to those used in SCORE (SCORE/CGPS), with and without HDL cholesterol included as predictor (see Supplementary material online, *Table S2*). In these well-calibrated models, the inclusion of HDL cholesterol did not provide incremental predictive value (see Supplementary material online, *Table S3*). The sensitivity and specificity of the 5% high-risk threshold were 0 and 100%, respectively, in both SCORE/CGPS and SCORE/CGPS-HDL models in the target population (age 40–65 at baseline). However, the sensitivity increased to 57 and 58% in the two models in the overall population, ignoring the age restriction given by using SCORE and SCORE-HDL (see Supplementary material online, *Table S3*).

Impact of lowering the cut-point for initiation of statin therapy

Net reclassification index increased progressively with stepwise lowering of the decision threshold from 5 to 1% (*Table 5*). For the combined endpoint of fatal CVD + non-fatal MI or stroke, the gain

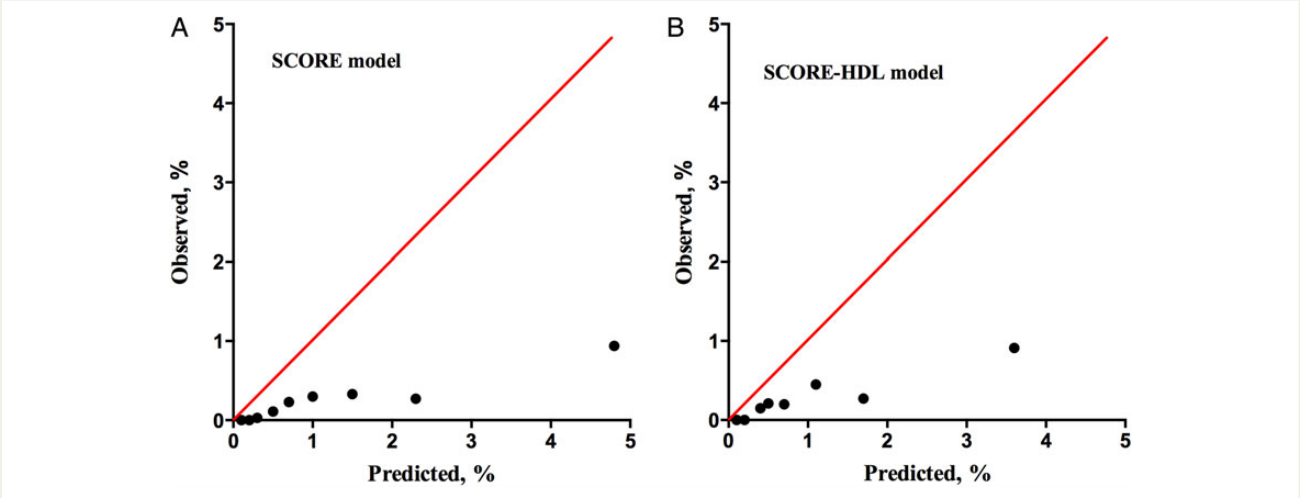

Figure 2 Calibration showing predicted vs. observed events. Both the original SCORE and the new SCORE-HDL models overestimated risk for fatal cardiovascular disease compared with Kaplan–Meier adjusted observed events. The straight line indicates perfect calibration (predicted events = observed events). Data represent men and women combined after 7 years of follow-up. SCORE, Systematic COronary Risk Evaluation; HDL, high-density lipoprotein.

Table 3 Predictive performance of original SCORE and new SCORE-HDL models for fatal CVD in the target population (cut-point: 5% 10-year risk of fatal CVD)

Model comparison	NRI (%)	ΔSensitivity (%)	ΔSpecificity (%)	Sensitivity (%)	Specificity (%)	c-Statistics	P/O[a]	HL-χ^{2a}
Men and women								
SCORE	Ref	Ref	Ref	42	91	0.809	5.0	237
SCORE-HDL	−12 ($P = 0.02$)	−16 ($P = 0.002$)	+4 ($P < 0.0001$)	26	95	0.808 ($P = 0.96$)	3.6	146
Men								
SCORE	Ref	Ref	Ref	49	83	0.736	4.9	
SCORE-HDL	−7 ($P = 0.23$)	−13 ($P = 0.01$)	+7 ($P < 0.0001$)	36	90	0.733 ($P = 0.85$)	4.0	
Women								
SCORE	Ref	Ref	Ref	23.5	97	0.850	5.5	
SCORE-HDL	−21 ($P = 0.07$)	−24 ($P = 0.04$)	+2 ($P < 0.0001$)	0	99	0.837 ($P = 0.81$)	3.1	

NRI, net reclassification index (reclassifications across the 5% high-risk threshold); SCORE, Systematic COronary Risk Evaluation; HDL, high-density lipoprotein; CVD, cardiovascular disease.
[a]For estimation of P/O (predicted/observed) and Hosmer–Lemeshow (HL) χ^2 coefficient, we calculated 7-year risk of fatal CVD and compared predicted with Kaplan–Meier adjusted observed event rates.

Table 4 Predictive performance of original SCORE and new SCORE-HDL models for fatal CVD + non-fatal MI or stroke in the target population (cut-point: 5% 10-year risk of fatal CVD)

Model comparison	NRI (%)	ΔSensitivity (%)	ΔSpecificity (%)	Sensitivity (%)	Specificity (%)	c-Statistics
Men and women						
SCORE	Ref	Ref	Ref	26	91	0.714
SCORE-HDL	−5 ($P < 0.0001$)	−9 ($P < 0.0001$)	+4 ($P < 0.0001$)	16	95	0.712 ($P = 0.75$)
Men						
SCORE	Ref	Ref	Ref	37	84	0.702
SCORE-HDL	−4 ($P = 0.03$)	−10 ($P < 0.0001$)	+7 ($P < 0.0001$)	26	90	0.709 ($P = 0.14$)
Women						
SCORE	Ref	Ref	Ref	10	97	0.686
SCORE-HDL	−5 ($P = 0.001$)	−8 ($P < 0.0001$)	+2 ($P < 0.0001$)	2	99	0.686 ($P = 0.92$)

NRI, net reclassification index (reclassifications across the 5% high-risk threshold); SCORE, Systematic COronary Risk Evaluation; HDL, high-density lipoprotein; CVD, cardiovascular disease; MI, myocardial infarction.

in NRI was significant for men and women separately (see Supplementary material online, *Tables S4–S5*).

Sensitivity analysis

In the sensitivity analyses, we first re-assessed the predictive performance of SCORE and SCORE-HDL using a broader definition of fatal CVD by also including SCORE endpoints (defined by ICD codes) registered as 'contributing cause' of death. One hundred and seventeen deceased fulfilled this outcome definition (81 men and 36 women). Still, both SCORE and SCORE-HDL overestimated risk. Also, SCORE-HDL did not improve discrimination for this endpoint compared with SCORE but reduced the sensitivity by 13%, yielding a negative NRI of −9% (see Supplementary material online, *Table S6*). Next, we expanded the endpoint definition further by also including individuals who died within 30 days after a MI or stroke recorded in the Danish Patient Registry, but without any SCORE endpoint (defined by ICD codes) recorded in the Danish Cause of Death Registry. Using this endpoint, there were 132 fatal CVD events (88 men and 44 women). As before, SCORE and SCORE-HDL still overestimated risk. Likewise as before, SCORE-HDL did not improve discrimination, but reduced sensitivity by 13% yielding a negative NRI of −9% (see Supplementary material online, *Table S7*). Finally, we re-assessed the predictive performance of SCORE and SCORE-HDL without excluding the 1509 individuals receiving statin therapy at baseline examination. The number of fatal CVD events (underlying cause of deaths) was 67 (50 men and 17 women). The results were similar to those obtained from the analyses where statin users were excluded. SCORE-HDL did not improve the discriminative performance, but decreased the sensitivity for fatal CVD,

Table 5 Impact of lowering the decision threshold in the target population of men and women combined (age 40–65)

Cut-point (10-year risk)	Fatal CVD (n = 62)			Fatal CVD + non-fatal MI or stroke (n = 767)		
	NRI (%)	ΔSensitivity (%)	ΔSpecificity (%)	NRI (%)	ΔSensitivity (%)	ΔSpecificity (%)
SCORE						
5%	Ref	Ref (42% sens)	Ref (91% spec)	Ref	Ref (26% sens)	Ref (91% spec)
4%	+2 ($P = 0.51$)	+6 ($P = 0.04$)	−4 ($P < 0.0001$)	+6 ($P < 0.0001$)	+11 ($P < 0.0001$)	−4 ($P < 0.0001$)
3%	+5 ($P = 0.31$)	+16 ($P = 0.002$)	−11 ($P < 0.0001$)	+12 ($P < 0.0001$)	+23 ($P < 0.0001$)	−11 ($P < 0.0001$)
2%	+8 ($P = 0.26$)	+31 ($P < 0.0001$)	−23 ($P < 0.0001$)	+14 ($P < 0.0001$)	+36 ($P < 0.0001$)	−22 ($P < 0.0001$)
1%	+11 ($P = 0.23$)	+53 ($P < 0.0001$)	−42 ($P < 0.0001$)	+11 ($P < 0.0001$)	+53 ($P < 0.0001$)	−42 ($P < 0.0001$)
SCORE-HDL						
5%	Ref	Ref (26% sens)	Ref (95% spec)	Ref	Ref (17% sens)	Ref (95% spec)
4%	+7 ($P = 0.09$)	+10 ($P = 0.01$)	−3 ($P < 0.0001$)	+4 ($P < 0.0001$)	+7 ($P < 0.0001$)	−3 ($P < 0.0001$)
3%	+13 ($P = 0.03$)	+21 ($P = 0.0003$)	−8 ($P < 0.0001$)	+12 ($P < 0.0001$)	+20 ($P < 0.0001$)	−8 ($P < 0.0001$)
2%	+17 ($P = 0.03$)	+34 ($P < 0.0001$)	−17 ($P < 0.0001$)	+15 ($P < 0.0001$)	+32 ($P < 0.0001$)	−17 ($P < 0.0001$)
1%	+26 ($P = 0.009$)	+63 ($P < 0.0001$)	−37 ($P < 0.0001$)	+18 ($P < 0.0001$)	+54 ($P < 0.0001$)	−36 ($P < 0.0001$)
SCORE/CGPS						
5%	Ref	Ref (0% sens)	Ref (100% spec)	Ref	Ref (0% sens)	Ref (100% spec)
4%	0	0	0	0	0	0
3%	+11 ($P = 0.01$)	+11 ($P = 0.008$)	−0 ($P < 0.0001$)	+3 ($P < 0.0001$)	+4 ($P = 0.0003$)	−0 ($P < 0.0001$)
2%	+15 ($P = 0.003$)	+18 ($P = 0.002$)	−2 ($P < 0.0001$)	+6 ($P < 0.0001$)	+8 ($P < 0.0001$)	−2 ($P < 0.0001$)
1%	+30 ($P = 0.0003$)	+40 ($P < 0.0001$)	−11 ($P < 0.0001$)	+19 ($P < 0.0001$)	+29 ($P < 0.0001$)	−10 ($P < 0.0001$)

NRI, net reclassification index (reclassifications across a lower cut-point compared with the 5% high-risk threshold); SCORE, Systematic COronary Risk Evaluation; CGPS, Copenhagen General Population Study; HDL, high-density lipoprotein; CVD, cardiovascular disease; MI, myocardial infarction; sens, sensitivity; spec, specificity.

yielding a negative NRI of −12% (see Supplementary material online, *Table S8*).

Time trend for cardiovascular risk factors and use of preventive medication

For all participants included in the CGPS between 2004 and 2012, the period during which we collected CVD endpoints, we observed decreases in smoking prevalence from 28% in 2004 to 10% in 2012 and increases in statin use from 7% in 2004 to 15% in 2012 (see Supplementary material online, *Table S9*).

Discussion

To the best of our knowledge, this is the first study to directly compare the clinical performance of the SCORE and SCORE-HDL risk prediction models. In a contemporary large-scale population-based cohort from a 'low-risk' European country, the newly recommended SCORE-HDL model did not improve discrimination compared with the SCORE model, but lowered the sensitivity of the 5% high-risk threshold and resulted in a negative NRI. Using well-calibrated risk prediction models, none of those who died of CVD in the target population passed the high-risk threshold, and HDL cholesterol did not provide incremental predictive value beyond traditional SCORE-based risk assessment. Finally, lowering the 5% decision threshold improved sensitivity and NRI substantially.

Incremental predictive value of high-density lipoprotein cholesterol

When originally tested in the SCORE dataset, the ratio of total to HDL cholesterol was not superior to total cholesterol alone as predictor for fatal CVD.[7] More recently, the incremental value of adding HDL cholesterol alone as an independent variable was evaluated and found worth recommending.[2,3,10] However, in these analyses the SCORE-HDL model was not compared with the original SCORE model, but with a SCORE-like Cox model with different β-coefficients for risk factors (sex specific instead of sex neutral) and different baseline survival function[10] than the original SCORE model. Nevertheless, no significant improvement in NRI was seen after incorporation of HDL cholesterol except for women from high-risk countries.[10] In the present study, when tested head-to-head for the first time, SCORE-HDL decreased the sensitivity substantially and, surprisingly, resulted in a negative NRI compared with SCORE. This was true for both fatal CVD (endpoint defined by SCORE) and fatal CVD + non-fatal MI or stroke which is more common and stronger related to HDL cholesterol. Thus, compared with SCORE, the SCORE-HDL model deteriorated classification of risk. Notably, among women, the sensitivity of the 5% high-risk threshold was zero for fatal CVD and 2% for fatal CVD + non-fatal MI or stroke, indicating that very few women will qualify for intensified prevention if the SCORE-HDL model is used.

Why SCORE overestimated risk more than SCORE-HDL is not clear, but could be due to different background CVD mortality in the derivation cohorts and/or different methods to measure HDL

cholesterol (precipitation methods then vs. direct methods today), as discussed by Cooney *et al.*[10] and Langlois *et al.*[13]

Finally, we found no incremental predictive value of HDL cholesterol when added to well-calibrated risk models developed from the CGPS cohort. This possibly reflects that the proportion of fatal CHD, which is strongly related to HDL cholesterol, to all fatal CVD was much lower in the CGPS than in the older SCORE cohorts (34 vs. 70%).

Overestimation of risk in 'low-risk' European countries

The recent guidelines inform that the high-risk model underestimates risk in many mostly Eastern European countries,[3] but it is less well recognized that the low-risk model may overestimate risk in countries classified as 'low risk'. Indeed, evidence from recent studies suggests that the low-risk SCORE model overestimates risk in several European populations.[14–18] Our data indicate that this is also the case for Denmark, a country that originally contributed data to the development of the high-risk model but now is recommended to use the low-risk model because of declining CVD mortality.[3] Despite this, the low-risk model overestimated risk substantially in CGPS. Noteworthy, SCORE was developed to predict fatal CVD, defined as the underlying cause of death attributed to specific ICD codes.[7] To exclude the possibility that our findings could be due to under-reporting and/or miscoding of the ICD-defined outcomes predicted by SCORE, we expanded the endpoint definition in the sensitivity analyses. Using these more inclusive endpoint definitions, the SCORE low-risk model continued to overestimate risk. Finally, using SCORE/CGPS models in a contemporary Danish population, no individuals undergoing risk assessment between 40 and 65 year of age would be eligible for intensified prevention, that is, if the criteria remains $\geq$5% 10-year risk of fatal CVD and if SCORE is well-calibrated as recommended. Thus, it may be time for European guidelines to consider lower cut-points for initiation of statin therapy and/or to include CVD morbidity in the predicted endpoint. The differences that may exist between studies in defining non-fatal CVD can be used as an argument for not extending risk estimation to non-fatal events; however, the very low fatal CVD event rate observed in many contemporary European countries is an argument against continued use of fatal CVD alone as the sole endpoint.

It should be noted that only 18% (62/339) of the fatal CVD events the European guidelines are intended to prevent occurred in people belonging to the target population defined by SCORE, that is, age 40–65 at the time of risk assessment. Thus, future European guidelines should also consider people above age 65.

Clinical implication

Our results have important implications for primary prevention of CVD in 'low-risk' European countries. First, the number of persons eligible for intensified prevention (risk $\geq$5%) depends critically on the model used for risk assessment. Second, although SCORE and SCORE-HDL demonstrate similar ability to discriminate between cases and non-cases, substantially fewer people destined for CVD event will be offered intensified prevention if the new SCORE-HDL model is used instead of the original SCORE model. Using the SCORE-HDL model, the sensitivity of the 5% high-risk threshold in women is close to zero for both fatal CVD and fatal CVD + non-fatal MI or stroke. Third, recalibration of the SCORE models to fit the declining CVD mortality may phase out intensified primary prevention if the 5% high-risk threshold remains the trigger for treatment and if only those of age 40–65 are considered.

Strength and limitations

A potential limitation is the relatively few fatal events. However, intuitively this limitation should lead to loss of power rather than generation of spurious findings. Another limitation of our study is that we only studied white individuals, and thus, our results do not necessary apply to other ethnicities; however, we are not aware of data to suggest that our results are restricted to whites only. A potential confounder is use of preventive medication at baseline and during follow-up. Interestingly, in the CGPS between 2004 and 2012, the period during which we collected fatal CVD + non-fatal MI and stroke endpoints, we observed decreases in smoking prevalence and increases in statin use which may help explain the low number of fatal CVD endpoints observed in Denmark during this period. Finally, as follow-up in the CGPS was $<$10 years, we had to slightly modify the baseline survival function to calculate 7-year risk of fatal CVD to assess SCORE calibration. However, as the SCORE models are based on a parametric Weibull survival function, these modifications were easily done in Step 1 of the SCORE algorithms.[7]

Our study has several strengths. First, we used a large contemporary cohort, which is close to the proposed target population for SCORE and SCORE-HDL. Second, we were able to carry out analyses using the approach recommended by the European guidelines and the SCORE investigators.[2,3,7,9,10] Third, although some misclassification of CVD deaths might occur, we carried out sensitivity analyses that showed that our results were robust to potential sources of misclassification error.

Conclusion

In a contemporary 'low-risk' European population, both SCORE and SCORE-HDL strongly overestimated risk of fatal CVD. Surprisingly, the SCORE-HDL model did not provide incremental predictive value beyond traditional SCORE risk assessment, but in contrast deteriorated classification of risk by placing more individuals who develop CVD in the low risk category. Our results suggest that the SCORE model might be preferable to the SCORE-HDL model in 'low-risk' European countries, particularly among women. Future guidelines should consider to lower the threshold for initiation of statin therapy and to focus more on CVD morbidity and people above age 65.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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