Should non-cardiovascular mortality be considered in the SCORE model? : findings from the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort

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Should non-cardiovascular mortality be considered in the SCORE model? Findings from the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort

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Abstract Competing non-cardiovascular related deaths were not accounted for in the Systematic Coronary Risk Evaluation (SCORE) model. In this study we assessed the impact of non-cardiovascular related deaths on the prognostic performance and yield of the SCORE model. 5,752 participants from the Prevention of Renal and Vascular End stage Disease cohort aged 40 years and older who were free of atherosclerotic cardiovascular disease (CVD) at baseline were included. A cause-specific hazards (CSH) CVD-related mortality prediction model that accounted for non-CVD-related deaths was developed. The prognostic performance of this model was then compared with a refitted SCORE model. During a median follow-up period of 12.5 years, 139 CVD and 495 non-CVD-related deaths were reported. Discriminatory performance was comparable between the models ($C$-index $= 0.64$). The models showed good calibration although the CSH model underestimated risk in the highest decile while the refitted SCORE model showed overestimation. The CSH model classified more non-events into the low risk group compared to the refitted SCORE model ($n = 51$), yet it was accompanied by a misclassification of six events into the low risk group. The refitted SCORE model classified more individuals as high risk. However, the potential overtreatment that may result from utilizing the refitted SCORE model, compared with the CSH model, still falls within acceptable limits. Our findings do not support the incorporation of non-cardiovascular mortality into the estimation of total cardiovascular risk in the SCORE model.

Keywords Competing risks · Total cardiovascular risk · SCORE · Primary prevention · Risk misclassification · Overtreatment

Introduction

European guideline on cardiovascular disease prevention in clinical practice recommends the utilization of total cardiovascular risk to guide the initiation of primary prevention interventions targeting atherosclerotic cardiovascular disease (CVD) in the general population [1]. This recommendation is primarily based on evidence suggesting that the higher the risk, the greater the benefit from interventions will be, thus justifying the need for the initiation of intensive risk factor management at higher levels of predicted CVD-related mortality risk [1, 4–8]. In particular, if the predicted 10-year risk of CVD-related mortality exceeds 5%, individuals are classified as being at high cardiovascular risk and initiation of intensive risk factor management interventions is strongly recommended [1]. The Systematic Coronary Risk Evaluation (SCORE) model is utilized in many European countries to facilitate total cardiovascular risk estimation in apparently healthy individuals in the general population. It estimates the 10-year absolute risk of CVD-related mortality using traditional cardiovascular risk factors [8].

Despite the fact that SCORE risk charts can be easily applied in daily clinical practice and are widely used, the
approach utilized to derive absolute risk estimates is not without methodological limitations. One of these is the fact that occurrence of non-CVD-related deaths was not accounted for in the development of the current version of the SCORE model. Unless explicitly accounted for in the statistical analysis, the presence of non-CVD-related death as a competing risk can result in serious overestimation of absolute cardiovascular risk, which in turn may result in overestimation of the expected benefit of intensive risk factor management [9–13]. This can potentially result in overtreatment, particularly in older individuals who are more likely to be in the high-risk group while also having a high risk of death from non-CVD-related causes [11, 14, 21]. This will have significant implications from both medical (e.g., side effects of medications, pill burden) and health economic (e.g., cost of medications, increased burden on practitioners) perspectives.

Although in theory it is clear that competing non-CVD-related deaths could lead to overestimation of total cardiovascular risk, the consequences of this overestimation on the prognostic performance and yield of the SCORE model had not been evaluated directly. The main objective of this study was to assess the potential impact of competing non-CVD-related deaths on the prognostic ability and yield of the SCORE model by utilizing competing risks methodology.

Methods

Study population

Data from the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort were utilized in this study. PREVEND is a population-based prospective cohort study primarily aimed at investigating the natural course of increased levels of urinary albumin excretion (UAE) and its association with long-term renal and cardiovascular outcomes in the general population. Details of the design and methodology of the study have been published elsewhere [15–18]. In summary, in the period 1997–1998, all inhabitants of the city of Groningen, the Netherlands, aged 28–75 years were sent a one-page postal questionnaire and a vial to collect an early morning urine sample (n = 85,421). Of these individuals, 40,856 (47.8%) responded and sent a vial to a central laboratory where urinary albumin and creatinine concentrations were measured. After exclusion of those with IDDM and pregnant women, all individuals with a UAE ≥ 10 mg/L (n = 7,768) and a randomly selected control group with a UAE < 10 mg/L (n = 3,395) were invited to visit an outpatient clinic for further investigations (total n = 11,163). Of these, 6,000 participants with UAE ≥ 10 mg/L and 2,592 with UAE < 10 mg/L completed the total screening program. These 8,592 individuals comprise the actual PREVEND study cohort. The screening program at the outpatient clinic consisted of two different visits. Participants completed a self-administered questionnaire on demographics, cardiovascular and renal history and the use of medication for diabetes, hypertension or hyperlipidemia. Anthropometric measurements and several laboratory and electrocardiographic assessments were also performed during these visits. These individuals were followed-up with a series of surveys every 3–4 years for the occurrence of several cardiovascular and renal outcomes, the last of which was conducted in 2010.

For this particular study, we included individuals from the PREVEND cohort aged 40 years and older who were free of CVD at baseline. We excluded individuals with a previous history of coronary heart disease (CHD) (n = 372), cerebrovascular accident (CVA) (n = 76) or surgery on leg arteries (n = 70) at baseline. In total, 5,752 individuals remained in the analyses.

Covariates and measurements

We used the baseline levels of covariates utilized in the SCORE model [8]. These included traditional cardiovascular risk factors; sex, age, smoking, systolic blood pressure (SBP) and total serum cholesterol. Smoking was defined as current smoking or smoking cessation within the previous year. Blood pressure was measured in supine position, every minute, with an automatic Dinamap XL Model 9300 series device (Johnson and Johnson, Medical Inc., Arlington, TX) during both visits (for 10 and 8 min, respectively). SBP was calculated as the mean of the last two measurements during the two visits. Serum cholesterol levels were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA), an automatic enzymatic method. Low-density lipoprotein cholesterol (LDL-C) levels were estimated using the Friedewald’s method [19]. Hypertension was defined as having SBP ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and/or use of anti-hypertensive medication. Hypercholesterolemia was defined as serum cholesterol ≥ 6.5 mmol/L or use of lipid-lowering medications.

Outcome and definitions

The primary outcome of this study was time-to-CVD-related mortality. Data on mortality were retrieved through the municipal registry. Cause of death was obtained by linking the death certificate to the primary cause of death as coded by Statistics Netherlands (CBS). These data were coded according to the International Classification of Diseases version 10 (ICD-10). CVD-related mortality was divided into CHD-related mortality or atherosclerotic
non-CHD-related mortality. CHD-related mortality was defined as death secondary to acute myocardial infarction (I21–23), acute and subacute ischaemic heart disease (I24–25), cardiac arrest (I46), other cardiac arrhythmias (I49), heart failure (I50). Atherosclerotic non-CHD-related mortality was defined as death secondary to subarachnoid hemorrhage (I60), intracerebral hemorrhage (I61), other intracranial hemorrhage (I62), occlusion or stenosis of the precerebral or cerebral arteries (I63–66), other cerebrovascular diseases (I67), sequelae of cerebrovascular diseases (I69), atherosclerosis (I70), aortic aneurysm and dissection (I71), arterial embolism and thrombosis (I74). Deaths due to all other causes were treated as non-CVD-related. Cause of death was unspecified in 1.3 % (n = 8) of cases. Around 12 % (n = 704) of the study participants were lost to follow-up because they moved to an unknown destination and were censored on the date they were removed from the municipal registry.

Statistical analysis

Baseline characteristics were summarized with descriptive statistics; categorical variables with proportions, normally distributed continuous variables with mean ± SD, and those variables with skewed distributions with median and interquartile range. Actual 10-year risk of CVD and non-CVD-related mortality were estimated using the non-parametric estimate of the cumulative incidence function [9].

To assess the potential impact of competing non-CVD-related deaths on the prognostic performance of the SCORE model, two main steps were followed. In the first step, we obtained each individual’s 10-year predicted risk of CVD-related mortality under two models; the SCORE model and a competing risks model based on the cause-specific hazards (CSH) approach. As it is difficult to make direct comparison of two non-nested models developed in different study populations, we started by refitting the SCORE model in the PREVEND cohort. Model refitting is a procedure that allows for the adjustment of the performance of an existing model to a different study population [20]. The SCORE was based on separate models for CHD and atherosclerotic non-CHD-related mortality that were developed with the Weibull proportional hazards modeling approach [8]. The models had two components; a baseline hazard function (parameterized by shape (p) and scale (α) parameters) and relative risks associated with each risk factor. Baseline hazard functions were assumed to be different for men and women while relative risk estimates associated with each risk factor were considered to be similar for both sexes. To this end, stratified Weibull proportional hazards models were fit, that yielded estimates of relative risks derived from the whole population and sex-specific parameters for the baseline hazard functions. Age, rather than time under follow-up, was utilized as the time scale for the hazard functions. Consequently, age was not included in the models as a separate covariate. For this study, we utilized a model structure similar to that used in the SCORE model. The model refitting procedure involved modifying parameter estimates of the baseline hazard functions and relative risks associated with each risk factor for the CHD and atherosclerotic non-CHD related mortality models with estimates derived from our study population. Subsequently, 10-year risks of CHD and atherosclerotic non-CHD-related mortality were estimated using the standard survival analysis techniques. These two functions were combined to obtain 10-year risk of CVD-related mortality. In this approach, non-CVD-related deaths were treated as censored observations. For the competing risks model, three separate cause-specific proportional hazards Weibull models for CHD, atherosclerotic non-CHD and non-CVD-related mortality were fit using the same risk factors and model structure utilized in the SCORE model. Individual 10-year risks of CHD and atherosclerotic non-CHD related mortality were then estimated with the cumulative incidence function, which accounted for non-CVD-related deaths. This required incorporation of the cause-specific hazard function of non-CVD-related mortality into the estimation of 10-year cumulative incidence functions of both CHD and atherosclerotic non-CHD related mortality. In addition, failures from atherosclerotic non-CHD-related death were treated as a competing risk for the estimation of 10-year risk of CHD-related mortality and the latter for atherosclerotic non-CHD-related mortality. These two cumulative incidence functions were then summed up to obtain 10-year risk of CVD-related mortality. We observed a statistically significant interaction between total cholesterol and lipid lowering medication use at baseline and hence, this was accounted for in both the refitted SCORE and competing risks models. The competing risks model will be referred to as the CSH model for the rest of this paper. Details of the specific procedures utilized to obtain individual 10-year risks of CVD-related mortality based on the two models are provided in Appendix 2.

In the second step, the prognostic performance of the refitted SCORE and CSH models was compared by evaluating various measures of model performance. Calibration was assessed by plotting average predicted risk against average observed risk within each decile of 10-year predicted risk of CVD-related mortality. Discrimination was assessed by calculating the C-index based on the Wolbers et al. [21] adapted definition of the risk set in the presence of competing risks. Optimism corrected estimates of the C-index were calculated using basic bootstrap technique. Predictiveness curves were plotted to evaluate model
predictiveness [22]. Risk reclassification graph was utilized to evaluate risk stratification [22, 23]. Separate risk reclassification graphs were plotted to assess movement of persons with and without the event of interest across risk thresholds of 5 and 10 %. According to the European guidelines on cardiovascular disease prevention in clinical practice, these thresholds are used to define high and very high risk groups, respectively. The impact of risk reclassification by the CSH model on treatment decisions was evaluated using criteria proposed by the same guideline for the initiation of lipid lowering treatment [1]. Individuals were classified into categories of “no treatment”, “treatment considered” and “treatment recommended” based on their absolute risk and baseline LDL-C levels. Two-sided $P$ value of $\leq 5 \%$ was considered significant. Estimates of hazard ratios and cumulative incidence were summarized with 95 % confidence intervals. The statistical analyses were performed using Stata version 11.0 (College Station, TX, USA) and R: A Language and Environment for Statistical Computing, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The baseline characteristics of the study population are presented in Table 1. Men were older, had higher blood pressure and higher triglyceride levels. No statistically significant differences were observed between men and women in the proportion of smokers and total or HDL cholesterol levels. During a median follow-up period of 12.5 years (interquartile range 0.79 years), 139 CVD-related deaths (83 CHD-related and 56 atherosclerotic non-CHD-related) and 495 non-CVD-related deaths were reported. The 10-year cumulative incidences of CVD and non-CVD-related mortality were 1.8 % (1.5–2.2 %) and 6 % (5.4–6.7 %), respectively (Fig. 4 in Appendix 1).

Cardiovascular mortality prediction models

Smoking and SBP were strong predictors of both CHD and atherosclerotic non-CHD related mortality. Similarly, these two risk factors were significantly associated with non-CVD-related mortality. The effect of smoking was strongest for CHD-related mortality. There was a statistically significant interaction between total cholesterol and lipid lowering medication use at baseline for CHD-related CVD mortality ($P = 0.013$). The effect of total cholesterol on CHD-related mortality was greater in those using lipid lowering medications (Table 2).

Evaluation of prognostic performance

Calibration and discrimination

Overall, both the refitted SCORE and CSH models yielded estimates of absolute risks that are in good agreement with observed risks. In the highest decile of predicted risk, however, the CSH model appeared to underestimate absolute risk while the refitted SCORE model showed slight overestimation (Fig. 1). The models showed comparable discriminatory performance; optimism-corrected C-indices were 0.637 and 0.638 for the refitted SCORE and CSH models, respectively. Similarly, these two risk factors were significantly associated with non-CHD-related mortality. Atherosclerotic non-CHD-related mortality were 1.8 % (1.5–2.2 %) and 6 % (5.4–6.7 %), respectively.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total, n = 5,752</th>
<th>Male, n = 2,882</th>
<th>Female, n = 2,870</th>
<th>$P$ value</th>
<th>Missing, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.3 ± 9.8</td>
<td>54.8 ± 10.0</td>
<td>53.8 ± 9.6</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Smoker, n(%)</td>
<td>2,114 (36.8)</td>
<td>1,080 (37.5)</td>
<td>1,034 (36.0)</td>
<td>0.254</td>
<td>21</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>2,270 (39.5)</td>
<td>1,257 (43.6)</td>
<td>1,013 (35.3)</td>
<td>&lt;0.001</td>
<td>118</td>
</tr>
<tr>
<td>Hypercholesterolemia, n(%)</td>
<td>1,690 (29.4)</td>
<td>795 (27.6)</td>
<td>895 (31.2)</td>
<td>0.004</td>
<td>153</td>
</tr>
<tr>
<td>AHM use</td>
<td>866 (15.1)</td>
<td>399 (13.8)</td>
<td>467 (16.3)</td>
<td>0.016</td>
<td>148</td>
</tr>
<tr>
<td>LLM use</td>
<td>189 (3.3)</td>
<td>87 (3.0)</td>
<td>102 (3.5)</td>
<td>0.310</td>
<td>148</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.9 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>&lt;0.001</td>
<td>69</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.7 ± 4.2</td>
<td>26.7 ± 3.6</td>
<td>26.6 ± 4.7</td>
<td>0.430</td>
<td>59</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>132.3 ± 21.1</td>
<td>136.2 ± 19.3</td>
<td>128.4 ± 22.0</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>76.0 ± 9.7</td>
<td>79.2 ± 9.3</td>
<td>72.7 ± 9.0</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.9 ± 1.1</td>
<td>5.9 ± 1.1</td>
<td>5.9 ± 1.1</td>
<td>0.276</td>
<td>47</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.3 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.4</td>
<td>0.060</td>
<td>130</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.2 [0.9–1.8]</td>
<td>1.4 [1.0–2.0]</td>
<td>1.1 [0.8–1.6]</td>
<td>&lt;0.001</td>
<td>129</td>
</tr>
</tbody>
</table>

Continuous variables were summarized with mean ± SD

$\text{AHM}$ anti-hypertensive medication, $\text{LLM}$ lipid lowering medication, $\text{BMI}$ body mass index, $\text{SBP}$ systolic blood pressure, $\text{DBP}$ diastolic blood pressure, $\text{HDL}$ high density lipoprotein, $\text{DM}$ diabetes mellitus

* Summarized with median and interquartile range
The refitted SCORE model classified 89.2% (n = 4,944) and 10.8% (n = 597) of individuals into the low and high risk categories, while the CSH model classified 90.3% (n = 5,001) and 9.7% (n = 540) of them into the low and high risk categories, respectively. The CSH model showed downward reclassification of non-events into lower risk categories. This was more pronounced at the 10% risk threshold (Fig. 3). At the 5% risk threshold, fifty-one non-events categorized as high risk by the refitted SCORE model were reclassified into low risk by the CSH model. However, this was accompanied by downward movement of six events who were in the high risk group based on the refitted SCORE model into the low risk.

Regarding treatment implications, the CSH model avoids immediate initiation of treatment with lipid lowering medications in 52 persons who do not experience the future event although this was accompanied by elimination of treatment in five individuals who eventually died from CVD-related causes (Table 3).

Table 2  Sex-stratified cause-specific proportional hazards Weibull models for the prediction of CHD, atherosclerotic non-CHD and non-CVD-related mortality

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>CHD mortality</th>
<th>Atherosclerotic non-CHD mortality</th>
<th>Non-CVD mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ (se)</td>
<td>HR</td>
<td>$P$ value</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.10 (0.23)</td>
<td>3.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, per mmHg</td>
<td>0.02 (0.01)</td>
<td>1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LLM use (offset at total cholesterol of 6 mmol/L)</td>
<td>0.63 (0.48)</td>
<td>1.90</td>
<td>0.184</td>
</tr>
<tr>
<td>Total cholesterol for persons with LLM use</td>
<td>1.04 (0.40)</td>
<td>2.85</td>
<td>0.007</td>
</tr>
<tr>
<td>Total cholesterol for persons with no LLM use</td>
<td>0.04 (0.10)</td>
<td>1.04</td>
<td>0.111</td>
</tr>
</tbody>
</table>

Shape parameter (p)

<table>
<thead>
<tr>
<th>Gender</th>
<th>$\beta$ (se)</th>
<th>$P$ value</th>
<th>$\beta$ (se)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>8.54 (1.16)</td>
<td>&lt;0.001</td>
<td>14.22 (1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>7.77 (1.25)</td>
<td>&lt;0.001</td>
<td>18.70 (1.21)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Scale parameter ($\alpha$)

<table>
<thead>
<tr>
<th>Gender</th>
<th>$\beta$ (se)</th>
<th>$P$ value</th>
<th>$\beta$ (se)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>168.46 (1.16)</td>
<td>&lt;0.001</td>
<td>311.26 (1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>203.70 (1.28)</td>
<td>&lt;0.001</td>
<td>274.60 (1.10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Fig. 1  Calibration plots of refitted SCORE (left) and CSH (right) models for the prediction of 10-year CVD-related mortality among individuals in the PREVEND cohort aged 40 years and older and free of CVD at baseline

Risk reclassification

The refitted SCORE model classified 89.2% (n = 4,944) and 10.8% (n = 597) of individuals into the low and high risk categories, while the CSH model classified 90.3% (n = 5,001) and 9.7% (n = 540) of them into the low and high risk categories, respectively. The CSH model showed downward reclassification of non-events into lower risk categories. This was more pronounced at the 10% risk threshold (Fig. 3). At the 5% risk threshold, fifty-one non-events categorized as high risk by the refitted SCORE model were reclassified into low risk by the CSH model. However, this was accompanied by downward movement of six events who were in the high risk group based on the refitted SCORE model into the low risk. Regarding treatment implications, the CSH model avoids immediate initiation of treatment with lipid lowering medications in 52 persons who do not experience the future event although this was accompanied by elimination of treatment in five individuals who eventually died from CVD-related causes (Table 3).
Discussion

In this study, we assessed the impact of competing non-CVD-related deaths on the prognostic performance and yield of the SCORE model by introducing a competing risks model based on the CSH approach and comparing its performance with a refitted SCORE model. Both models showed good calibration, although the refitted SCORE model calibrated better in the highest decile of risk. On the other hand, the discriminatory performance of the models was comparable. Assessment of risk reclassification indicated that the CSH model improved risk stratification among non-events compared to the refitted SCORE model, although it was associated with misclassification among events.

Total cardiovascular risk is promoted as a primary tool for guiding cardiovascular prevention strategies by major cardiovascular guidelines, including the European guidelines on cardiovascular disease prevention in clinical practice [1–3]. The SCORE risk charts are widely used in many European countries to facilitate total cardiovascular risk estimation in apparently healthy individuals in the general population [1]. However, an essential characteristic of older populations had not been accounted for in the development of the SCORE risk charts. Several studies indicated that non-CVD causes of death increasingly preclude CVD-related deaths with older age [14, 21, 24]. A similar finding was also observed in this study, as the 10-year risk of non-CVD-related mortality substantially exceeded that of CVD-related mortality. From a mathematical perspective, it is clear that the presence of non-CVD-related death as a competing risk results in overestimation of absolute risks unless appropriate methodology is applied [9].

The CSH model, which is a mathematically sound competing risk model that accounted for non-CVD causes...
of death, yielded well calibrated absolute risk estimates. In the highest decile of risk, however, the model appeared to underestimate absolute risks while the refitted SCORE model showed a lesser degree of absolute risk overestimation. Both models had a C-index of 0.64, indicative that ignoring non-CVD-related death did not have a noticeable impact on discriminatory accuracy. Although, in absolute terms, the discriminative ability of both models appears to be modest, it must be emphasized that Wolbers’ adapted C-index should not be interpreted the same way as the traditional C-index. The latter had been indicated to overestimate model accuracy in the presence of competing risks, particularly in situations with strong competing risks. Consequently, interpretation of the Wolbers’ adapted C-index on the same scale as the traditional C-index can potentially lead to underestimation of discriminatory accuracy in the competing risks setting [21]. A recently published simulation study has shown that to achieve improvement in discriminative accuracy with a cause-specific hazards model, the risk factors for the events of interest should only be weakly or reversely associated with the cause-specific hazard of the competing event [25]. In our situation, however, the strongest risk factors for CVD-related mortality (i.e. smoking and SBP) were also strongly associated with the cause-specific hazard of non-CVD-related mortality. This can partly explain the absence of improvement in discriminative accuracy with the CSH model. Additionally, as depicted by the predictiveness curves of the models (Fig. 2), adjusting for non-CVD related deaths had a minimal impact on the distribution of predicted risks in persons with no event and only a modest impact on the distribution of predicted risks in persons with the event of interest. The small difference in the distribution of predicted risks from the two models can further explain the comparability of the discriminatory accuracy of the models.

Compared to the refitted SCORE model, the CSH model reclassified 51 non-events from high risk to low risk. However, this came at the expense of misclassification of 6 persons with future events into the low risk. The European guideline on cardiovascular disease prevention recommends initiation of intensive risk factor management, including treatment with lipid lowering medications, based on a set of criteria that combine total cardiovascular risk and LDL-C levels [1]. Immediate treatment with lipid lowering medications is indicated in persons with estimated 10-risk of CVD-related morality $\geq$10 % (with the exception of persons with LDL-C levels <1.8 mmol/L) and those having risks ranging from 5 to 10 % and LDL-C levels $\geq$2.5 mmol/L. As a result, 557 individuals would qualify for immediate treatment with lipid lowering medications based on the refitted SCORE model. In contrast, immediate treatment with these medications is indicated in 518 individuals based on the CSH model. This model will avoid immediate treatment with lipid lowering medications in 57 individuals, 5 of whom experience the future events. Statins are the most commonly used lipid lowering medications in primary prevention. Around 20 % reduction in the risk of CVD-related mortality had been reported with the use of statins [5]. This will translate to numbers needed to treat (NNT) of 100 assuming a 5 % threshold of risk for treatment initiation, implying that up to 100 individuals may need to be treated to avoid a single CVD-related death. Based on NNT = 100, elimination of overtreatment in 52 persons with no event by the CSH model does not justify the avoidance of treatment in five persons with event. In addition, treatment with lipid lowering medications has been shown to be generally safe and effective. Serious side effects with medications like statins, including rhabdomyolysis are extremely rare [1, 5–7]. Finally, it has also been indicated that statins are cost-effective in primary prevention setting, particularly in high risk individuals [26]. When combined, these statements suggest that the gain with the CSH model in reducing overtreatment of persons with no event may not outweigh the excess of persons with the event that would not have been treated.

The findings of our study partly mirror the results reported by Koller et al. [14]. In their study, Koller and colleagues developed a CHD risk prediction model (CORE) for older European and U.S. persons using the Fine and Gray technique, taking non-CVD causes of death into account, and compared its performance with the Framingham point score (FPS) in the setting of cross-validation. Although the CORE model showed slightly better accuracy compared to the FPS, it did not show consistent

### Table 3 Lipid lowering treatment recommendations based on the refitted SCORE and CSH models

<table>
<thead>
<tr>
<th>Treatment categories&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Risk prediction model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Refitted SCORE model</td>
</tr>
<tr>
<td>Persons with event</td>
<td></td>
</tr>
<tr>
<td>Immediate treatment</td>
<td>61</td>
</tr>
<tr>
<td>Consider treatment</td>
<td>1</td>
</tr>
<tr>
<td>No treatment</td>
<td>34</td>
</tr>
<tr>
<td>Persons with no event</td>
<td></td>
</tr>
<tr>
<td>Immediate treatment</td>
<td>514</td>
</tr>
<tr>
<td>Consider treatment</td>
<td>11</td>
</tr>
<tr>
<td>No treatment</td>
<td>4,910</td>
</tr>
</tbody>
</table>

<sup>a</sup> Defined based on a combination of estimated risk of 10-year CVD-related mortality and LDL-C levels [1]: Immediate treatment Estimated risk $\geq$ 10 % (with the exception of persons with LDL-C levels <1.8 mmol/L) or 5 to 10 % and LDL-C levels $\geq$ 2.5 mmol/L; Consider treatment Estimated risk $\geq$ 10 % and LDL-C levels <1.8 mmol/L or 5 to 10 % and LDL-C levels $< 2.5 \text{ mmol/L}$, No treatment persons not fulfilling the above criteria.
improvement in risk stratification. The model classified more individuals into the lower risk categories compared to the FPS among Europeans, although similar findings were not observed among US participants. In addition, the gain in true-negative rate was accompanied by an increased false-negative rate among European men, which was the same pattern observed in our study. On the other hand, Wolbers et al. showed that CHD risk prediction models for women aged 55–90 years based on both cause-specific hazards and Fine and Gray techniques (which took non-CVD deaths into account) showed superior performance in terms of calibration and risk stratification compared to a standard Cox-regression model [20]. Similar to our study, however, there was no difference between the discriminatory performance of the models.

Our study has a limitation. The PREVEND cohort is primarily enriched with individuals having elevated levels of UAE. This may interfere with the generalizability of our findings to the general population. In particular, given raised UAE levels are more strongly associated with CVD-related mortality than non-CVD-related mortality, it is possible that the risk of death from non-CVD causes relative to death from CVD causes is underestimated in our study [18]. Subsequently, the effect of non-CVD-related death and the prognostic gain with a competing risks model that accounts for it can be greater in a general population cohort compared to the one observed in this study.

Conclusion

The occurrence of death from non-CVD related causes was not accounted for in many of the commonly utilized cardiovascular risk prediction models, including the SCORE model. Although it is theoretically clear that the presence of non-CVD related deaths as a competing risk results in overestimation of absolute risks, its practical consequence on the prognostic performance of the SCORE model had not been evaluated. In this study we assessed the potential consequence of non-CVD-related deaths by developing a mathematically sound competing risks model based on the CSH approach and comparing its performance with a refitted SCORE model. The CSH model yielded well-calibrated absolute risk estimates, although it showed underestimation in the highest decile of risk. The model also provided a valuable improvement in risk stratification among non-events, yet this was accompanied by misclassification among events. In conclusion, the refitted SCORE model classified more individuals as high risk compared to the CSH model although the potential overtreatment that may result from utilizing the refitted SCORE model, when compared with the CSH model, still falls within acceptable limits. Our findings do not support the incorporation of non-cardiovascular mortality into the estimation of total cardiovascular risk in the SCORE model.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard The PREVEND study was conducted in compliance with the Declaration of Helsinki and was approved by all local Ethics Committees. All participants of the study provided informed consent.

Appendix 1

See Fig. 4.

Appendix 2: Estimation of 10-year absolute risk of CVD-related mortality based on the refitted SCORE model

Step 1 Sex-stratified cause-specific proportional hazards Weibull models were fit for CHD and atherosclerotic non-CHD related deaths using person’s age as time-scale. For a cause of failure k, the models take the form:

$$\lambda_k(\text{age}; p, x, \beta, Z) = (p_k/z_k)(\text{age}/z_k)^{-1} \exp(\beta_k Z),$$

where $\lambda_k$ is the cause-specific hazard function for $k$th cause of failure, $\beta_k$ represents vector of regression...
coefficients of each risk factor for kth cause of failure and Z represents a person’s covariate value on the respective risk factor. P and x are sex-specific shape and scale parameters of the baseline hazard function for each cause of failure. Estimates of regression coefficients, $\beta_k$ and parameters of the baseline hazard functions, P and x, associated with these causes of failure are presented in the results (Table 2).

**Step 2** Estimation of survival functions for CHD and atherosclerotic non-CHD related mortality

\[ S_k(\text{age}) = \exp(-A_k(\text{age})), \quad K = 1, 2 \]

where, \(A_k(\text{age}) = \exp(\beta_k Z) \ast ((\text{age})/z_k) \gamma_k)\)

**Step 3** Estimation of 10-year survival probabilities for CHD and atherosclerotic non-CHD related deaths

Individual 10-year survival probability for each cause of failure, \(S_{k_{10}}\) was estimated from the survival functions in step 2 as a conditional probability of surviving up to \(10 + 10\) years given that the person survives up to \(\text{age}\).

\[ S_{k_{10}}(\text{age}) = S_k(\text{age} + 10)/S_k(\text{age}) \]

**Step 4** Estimation of 10-year risk of CVD-related mortality

\[ \text{Risk}_{\text{CVD}} = 1 - \exp(-\ln(S_{\text{CHD}_{10}}) + \ln(S_{\text{non}-\text{CHD}_{10}})) \]

Estimation of 10-year absolute risk of CVD-related mortality based on the CSH model

**Step 1** The same cause-specific proportional hazards Weibull models for CHD and atherosclerotic non-CHD-related mortality were used. In addition, a cause-specific hazards model which takes the form of equation in step 1 was fit for non-CVD-related mortality. The regression coefficients, \(\beta_k\), and the parameters of the baseline hazard function for this cause-specific hazards function are presented in Table 2.

**Step 2** Estimation of overall survival function

The cause-specific hazards functions of CHD, atherosclerotic non-CHD and non-CVD-related mortality were incorporated into the overall survival function, \(S(\text{age})\), through:

\[ S(\text{age}) = \exp \left( - \sum_{k=1}^{3} A_k(\text{age}) \right), \quad \text{where k = 1, 2, 3} \]

**Step 3** Estimation of 10-year absolute risks of CHD and non-CHD related deaths

The absolute risks of CHD and atherosclerotic non-CHD related mortality were estimated as cumulative incidence of each outcome at \(W = \text{age} + 10\) years given an individual is still a survivor at \(\text{age}\). The competing risk of non-CVD-related mortality was accounted for in this step as the cumulative incidence functions is determined by the cause-specific hazard functions of all the three causes of failure through the overall survival function \(S(\text{age})\). In addition, this also accounts for the competing risk effect of atherosclerotic non-CHD related deaths on CHD-related death and vice versa.

\[ I_k(\text{A} < T \leq \text{A} + W, D = K/T > \text{A}) = \int_{\text{A}}^{\text{A}+W} \hat{\lambda}_k(s)S(s)d(s) \]

\[ S(\text{A}) \]

where \(k = 1, 2\)

**Step 4** Estimation of 10-year risk of CVD-related mortality

\[ \text{Risk}_{\text{CVD}} = I_{\text{CHD}} + I_{\text{non}-\text{CHD}} \]

References


