SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions

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Summary

Aims: To derive and validate the SCORE2-Older Persons (SCORE2-OP) risk model to estimate 5- and 10-year risk of cardiovascular disease (CVD) in individuals aged over 65 years in four geographical risk regions.

Methods and results: Sex-specific competing risk-adjusted models for estimating CVD risk (CVD mortality, myocardial infarction, or stroke) were derived in individuals aged over 65 without pre-existing atherosclerotic CVD from the Cohort of Norway (28,503 individuals, 10,089 CVD events). Models included age, smoking status, diabetes, systolic blood pressure, total- and HDL-cholesterol. Four geographical risk regions were defined based on country-specific CVD mortality rates. Models were recalibrated to each region using region-specific estimated CVD incidence rates and risk factor distributions. For external validation, we analyzed data from 6 additional study populations (338,615 individuals, 33,219 CVD validation cohorts, C-indices ranged between 0.63 (95%CI 0.61-0.65) and 0.67 (0.64-0.69). Regional calibration of expected-versus-observed risks was satisfactory. For given risk factor profiles, there was substantial variation across the four risk regions in the estimated 10-year CVD event risk.

Conclusions: The competing risk adjusted SCORE2-OP model was derived, recalibrated and externally validated to estimate 5- and 10-year CVD risk in older adults (aged 65 or older) in four geographical risk regions. These models can be used for communicating the risk of CVD and potential benefit from risk factor treatment, and may facilitate shared decision making between clinicians and patients in CVD risk management in older persons.

Keywords: Risk prediction, risk assessment, cardiovascular disease, primary prevention, 10-year CVD risk, older persons.

Introduction

Risk of cardiovascular disease (CVD) increases with age.[1] The risk of non-CVD mortality generally *also* rises with age so that remaining life expectancy inevitably decreases with age. Hence, the treatment of important CVD risk factors needs to be carefully considered to balance the benefits and risks in this population. Meaningful treatment benefit is different in this population where life expectancy is limited,[2,3] while older persons are generally at high risk of developing adverse drug events and side effects.[4,5] It is thus important to identify those individuals who might benefit from preventive treatment.

For this purpose, CVD risk prediction models can be used to identify those at higher risk of CVD and those potentially benefiting the most from risk factor treatment.[6] These prediction models may also aid in patient-centred clinical decision making, taking into account other patient characteristics such as frailty, biological age and patient preferences.[7]

Most 10-year CVD risk prediction models generally have a poor performance in older individuals for several reasons.[8–11] First, the relationship between traditional risk factors and CVD attenuates with age,[12] and traditional risk prediction models do not take into account competing risk of non-CVD mortality, leading to overestimation of CVD risk and consequently overestimation of potential benefit from risk factor treatment in older persons.[3,13,14] This overestimation may lead to unnecessary treatment in older persons, polypharmacy, increased risk of drug interactions, adverse events, reduced quality of life and unnecessary costs.[15] To deal with short-comings of traditional risk models, an older person-specific risk score should be used. However, previously developed risk models for older persons only estimate risk of cardiovascular mortality while non-fatal events are also of importance (e.g. stroke and heart failure). Finally, previous models have not been extensively externally validated and shown to be applicable in different geographical risk regions where risk levels vary.[2,16,17]

We aimed to develop and validate a competing risk-adjusted model for individuals aged over 65 years without pre-existing CVD to estimate 5- and 10-year risk of incident CVD – the new SCORE2-Older Persons (SCORE2-OP). This risk model is calibrated to four different geographical risk regions using an approach based on aggregate level data that can be easily applied to further update the accuracy of risk predictions with changing CVD epidemiology in the future.

Methods

Study design

The SCORE2-OP project involved several interrelated components and data sources (**Figure 1**). The study design is closely related to the new SCORE2 model that estimates 10-year fatal and non-fatal CVD risk in individuals without previous CVD or diabetes aged 40-69 years.[18] First, model coefficients were derived in the Cohort of Norway (CONOR) study (**Supplementary Methods**).[19] This study population was selected because it is a large, representative population-based cohort and has previously been used for model derivation.[16,17,20] Second, the model was recalibrated to four geographical risk regions across Europe and beyond using estimated contemporary age- and sex-specific incidences and risk factor distributions. Third, external validation was performed in prospective cohorts from different risk regions. Finally, the model was applied to estimate individualized treatment benefit from blood pressure and cholesterol lowering to illustrate how SCORE2-OP can be used for treatment decision making in clinical practice.

Sources of data

This study derived the risk model coefficients from the prospective CONOR study,[19] and used combined data from several cohort studies and clinical trials for external validation and testing: the Atherosclerosis Risk in Communities (ARIC) study,[21] from which we used baseline data from visit 5 to include more individuals aged over 65 years; the Clinical Practice Research Datalink (CPRD);[22] the Hypertension in the Very Elderly Trial (HYVET);[23] the Multi-Ethnic Study of Atherosclerosis (MESA);[24] the "PROspective Study of Pravastatin in Elderly at Risk" (PROSPER) trial;[25] and the Systolic Blood Pressure Intervention Trial (SPRINT).[26,27] Details of the included studies can be found elsewhere and have been summarized in the **Supplementary Methods.** The current study was conducted using data from the target population of individuals aged 65 years or over. Individuals with a history of CVD (i.e. coronary heart disease, stroke, or peripheral artery disease) were excluded from analysis. All included studies comply with the Declaration of Helsinki, were approved by local institutional review boards and all participants provided written informed consent.

Endpoint definitions

The primary endpoint was a composite of the first fatal or non-fatal CVD events in each study participant, defined as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular mortality. Secondary endpoint included also hospitalization from heart failure (HF), as this is an important source of morbidity and loss in quality of life in older persons.

The CVD mortality component of the primary and secondary outcomes resembles the endpoint definition of the original SCORE project, including e.g. death from coronary heart disease, HF, stroke, and sudden death. An overview of the ICD-10 codes included in both the fatal and non-fatal component of the composite endpoint can be found in **Supplementary Table 1**. Deaths from non-CVD were treated as competing events. Follow-up time was defined as years until the first event, death, or end of the registration period.

Risk regions

The four risk regions (low, moderate, high, and very-high risk) were chosen based on the definition used in the newly developed SCORE2 risk model, according to the most recent overall age- and sex-standardized CVD mortality rates in all included countries (ICD 10 chapter IX, I00-I99). The following age-standardized rates were used for categorization: <100 CVD deaths per 100,000 (low risk), 100-149 CVD deaths per 100,000 (moderate risk), 150-299 CVD deaths per 100,000 (high risk), and ≥300 CVD deaths per 100,000 (very-high risk). The four geographical risk regions can be found in **Supplementary Figure 1** and **Supplementary Table 2**.

Statistical analysis

Details of statistical analysis are provided in **Supplementary Methods**. For model derivation, sex-specific coefficients were estimated in the CONOR study using competing risk-adjusted Fine and Gray proportional subdistribution hazards models. The models included the following pre-specified baseline predictors: age, current smoking, diabetes mellitus, systolic blood pressure (SBP), total cholesterol (TC),

and high density lipoprotein cholesterol (HDL-c). The risk factors were selected based on their predictive ability as well as availability in the derivation dataset and population statistics needed for model recalibration. Variable selection was not applied in order to prevent overfitting of the model to the derivation data (over-optimism). Age interaction terms were added as the effect of these risk factors may change with age.[28] Continuous predictors were truncated at the 1st and 99th percentile to minimize the influence of outliers in the model.[29] Whether the association of continuous predictors with the outcome variable was adequately explained with a log-linear relationship was assessed using the Akaike information criterion. Internal model performance was assessed with Harrell's C-index for discrimination, and visually with calibration plots of estimated versus observed risk in a random sample with replacement of the CONOR study population to account for overfitting. The model was then recalibrated internally for the risk of the secondary CVD endpoint including heart failure using age- and sex-specific multiplication factors, using the same model coefficients.

Risk models were recalibrated to risk regions using age- and sex-specific mean risk factor levels and CVD incidence rates.[30] Age-specific and sex-specific risk factor values were obtained from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC).[31,32] We obtained country-specific, age- and sex-specific CVD mortality rates reported by the World Health Organisation (WHO),[33] and estimated fatal and non-fatal CVD incidences by using age- and sex-specific multipliers derived in the SCORE2 project in multiple cohorts from the different risk regions with a total of 4,056,218 men and 3,869,443 women, with 732,471 CVD events.[18] The multipliers for fatal CVD to total CVD events per region are listed in **Supplementary Table 3**.

External validation was performed in 6 studies, including the ARIC, MESA, and CPRD cohorts, and the combined study populations of the HYVET, PROSPER and SPRINT trials (adding the trial treatment effect to account for differences in observed risk between the active treatment and control arm of the trials) as the separate trial populations have limited number of events in a short follow-up time. External model performance was assessed in terms of discrimination using Harrell's C-index, and in terms of model calibration using plots of observed versus estimated risks recalibrated using cohort-specific observed-versus-expected (O/E) ratios reflecting differences in baseline risk. SCORE2-OP was compared in terms of discrimination with the ASCVD (Atherosclerotic Cardiovascular Disease) risk calculator from

AHA/ACC, an internationally widely used risk model for the general population also including older persons.[34]

All analyses were conducted with R-statistic programming (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria). Our approach to model development and validation complies with PROBAST guidelines,[35] and TRIPOD.[36] The approaches used to handle missing data are described in the **Supplementary Methods**.

Absolute CV event risk reduction from risk factor treatment in older people

SCORE2-OP can be used to estimate individualized treatment effect estimations from cardiovascular risk factor treatment,[6] as described in detail in the **Supplementary Methods**. To estimate the effect of blood pressure lowering on CVD, average relative treatment effects from large meta-analyses were added to SCORE2-OP. We estimated absolute treatment effect from blood pressure lowering to the target of <140mmHg in older persons with hypertension from the HYVET and SPRINT trials,[26,37] using a hazard ratio (HR) of 0.80 per 10 mmHg SBP reduction from a large meta-analysis.[38] For the effect of lipid lowering, a HR 0.78 per 1 mmol/L LDL-cholesterol lowering was used,[39] and the absolute risk reduction (ARR) of lowering LDL-cholesterol to <2.6 mmol/L was estimated in participants with hypercholesterolemia from the PROSPER trial.[25] The ARR is defined as the baseline ("untreated") CVD risk minus the CVD risk with added risk factor management.

Results

A total of 211,184 women and 155,934 men aged 65 years or over from seven studies were included in the analysis for model derivation and validation. Study and baseline characteristics of all study populations are presented in **Table 1**.

Model derivation and recalibration

A total of 10,089 non-fatal and fatal CVD events occurred in 305,640 person years of follow-up in the 28,503 participants included from the CONOR study, the derivation data. SCORE2-OP model coefficients and subdistribution hazard ratios for CVD events are shown in **Table 2**. **Supplementary Figure 2** shows the change in the effect of model predictors with increasing age.

In the internal validation set of the CONOR study, the 10-year estimated risk showed good agreement with the 10-year observed risk over all deciles for all outcomes of interest (**Supplementary Figure 3**). C-index were 0.66 (95% confidence interval [95% CI] 0.65-0.66) for CVD events, and 0.65 (95% C 0.65-0.66) for CVD events including heart failure. The age- and sex-specific multiplication factors for estimating the risk of CVD events including heart failure can be found in **Supplementary Table 4**.

Age and sex-specific 10-year mortality CVD rates and derived incidence rates are shown for each region in **Supplementary Figure 4**. The age-specific and sex-specific mean risk factor levels and estimated CVD event rates used for recalibration are presented by region in **Supplementary Table 5**. After regional recalibration, SCORE2-OP estimated risks based on mean risk factor levels agreed well with the regional estimated CVD event incidence in the four risk regions across age-groups (**Supplementary Figure 5**).

In the external validation study populations, a total of 33,219 primary outcome events were observed in 338,615 individuals in 2,259,933 person-years of follow-up. The external validation showed C-index for discrimination (**Figure 2**) ranging between 0.63 (95% CI 0.61-0.65) and 0.67 (95% CI 0.64-0.69). Calibration plots per study population after accounting for differences in baseline risk are shown in **Supplementary Figure 6**. For the secondary CVD endpoint including heart failure, the external C-index ranged between 0.63 (95% CI 0.61-0.65) and 0.67 (95% CI 0.65-0.69). When we applied the recalibrated SCORE2-OP models from each risk region to individual risk factor data from participants from ARIC and MESA, the risk distribution varied greatly between risk regions (**Figure 3**). Comparison of SCORE2-OP and the ASCVD risk engine can be found in **Supplementary Table 6**. C-index for SCORE2-OP were comparable to or higher than for ASCVD in the other study populations. In the external validation cohorts, the time-dependent ROC were comparable to or higher than Harrell's C-index (**Supplementary Table 7**).

Two-dimensional risk charts of SCORE2-OP for all four risk regions are shown in the **Supplementary Appendix**, for practical purposes displayed according to non-HDL rather than total cholesterol and HDL-

cholesterol. We have also added risk charts for the estimated 5-year risk, as this may fulfil a clinical need especially in the very old. The estimated absolute risk for a given age and combination of risk factors differed substantially across regions. For example, the estimated 10-year CVD risk for a 75-year-old male smoker with a systolic blood pressure of 150 mmHg, and a non-HDL cholesterol of 4.5, ranged from 16% in a low risk country to 37% in a very high-risk country (**Supplementary Figure 7**). Similarly, the 10-year risk for a 75-year-old woman with the same risk factor profile ranged from 14% in a low risk country to 44% in a very high-risk country. A sensitivity analysis taking into account uncertainty around individual predictions is described in the **Supplementary Methods** and shown in **Supplementary Figures 8.**

Absolute 10-year CVD event risk reduction from risk factor treatment in older people

The distribution of individual estimated 10-year CVD risk and associated ARR for blood pressure lowering therapy when targeting an SBP of <140 mmHg in 5,579 older persons with hypertension (SBP at baseline >140) in the SPRINT and HYVET blood pressure lowering trials is shown in **Figure 4**. The overall median estimated 10-year risk for CVD events was 30% (IQR 19-50%); for CVD events including heart failure, this was 36% (22-55%). The overall median estimated individual 10-year ARR from blood pressure lowering for the primary endpoint CVD events was 13% (IQR 4-21%); for CVD events including heart failure, this was 16% (IQR 5-23%). The distribution of the individual estimated 10-year CV event risk and associated ARR for lipid lowering therapy targeting an LDL-cholesterol <2.6 mmol/L in the PROSPER trial is shown in **Figure 5**. In these 3,051 older persons, the overall median estimated 10-year risk for CVD events was 18% (IQR 13-24%), for CVD events including heart failure this was 21% (16-28%); the overall median estimated individual 10-year ARR from lipid lowering for the primary CVD endpoint was 4% (IQR 3-6%); for the secondary CVD endpoint including heart failure this was 5% (IQR 3-7%).

Discussion

The current report describes the development, recalibration, and external validation of a new competing-risk adjusted model for older individuals aged over 65 years without pre-existing CVD – SCORE2-OP to estimate 5- and 10-year risk of incident CVD. There is a wide range in estimated individual CVD event

risk in older persons. Using SCORE2-OP, individualized effects of CVD risk factor treatment can be estimated, e.g. from blood pressure lowering or lipid lowering, which can be used for treatment decision making in clinical practice. The full clinical tool for individualized estimations will be made available to use in online calculators.

In the SCORE2-OP project investigators from 3 previously published older person CV risk algorithms joined forces by combining datasets and using advanced methodology for data analyses. The original SCORE O.P. model,[16] derived in more than 40,000 European older individuals (including participants from the CONOR study) estimated risk of fatal CVD. However, it did not take into account non-fatal CVD events, (such as non-fatal stroke), that are clinically relevant in older persons, and was not adjusted for competing non-CVD mortality risk. Another risk model derived in CONOR is the NORRISK2 model for CVD risk estimation in elderly men and women up to age 79 years.[17] This risk score is competing risk adjusted, includes interaction terms with age, and was externally validated within Norway, but it was not recalibrated or externally validated outside Norway. Additionally, it was not derived specifically in older persons, including persons aged <65 years.[17,20] The older person-specific risk score derived in the PROSPER trial is competing-risk adjusted, and estimates the risk of fatal *and* non-fatal CVD events.[2] However, this risk model was derived in a relatively small study population from a randomized clinical trial, and did not include age interactions.

The SCORE2-OP model has combined these previous efforts and as such has several important strengths and advantages. First, the coefficients been derived in a large population-based cohort study, specifically in older persons. The model has been externally validated in populations with different baseline risks including both cohorts and trials from several countries. It was shown that SCORE2-OP recalibrated to the different risk regions corresponds well to the regional estimated WHO incidence rates, suggesting that calibration between estimated and observed risk is good for all risk regions. Although the discrimination in the external study populations is only moderate, the excellent calibration shows that the risk model can be used for clinical decision making and risk communication. For this purpose, calibration is arguably the more important metric than discrimination.[40] Use of the risk model in regions outside of the

included countries should be done with caution, as no validation has (yet) been performed outside of these regions.

Second, SCORE2-OP can be used to estimate the risk for the combined outcome of both fatal and non-fatal CVD events. Especially in older persons, non-fatal CVD events may be of clinical importance, as they may severely impact quality of life. The model also gives the option to include hospitalization for heart failure in the composite endpoint, which is an important source of morbidity in the older population.[41] In clinical practice, this may therefore be a very relevant endpoint for older persons especially when considering the consequences of heart failure for quality of life.

Third, the model is competing risk adjusted and includes age-interactions for all risk factors to account for differences in the relationship between risk factors and outcomes across different ages. This allows for estimations of 5- and 10-year prognosis truly tailored to the individual person.

Fourth, the model has been recalibrated using contemporary CVD rates currently available for the different risk regions using WHO data. The method used for systematic recalibration has previously been shown to give reliable estimations with good agreement between estimated and observed risks.[30] The recalibration methods avoid reliance on sparse or unreliable cohort or country-level data, providing stable recalibrations using age- and sex-specific CVD rates and risk factor levels of each risk region. Due to the flexible recalibration approach based on the most recent registry data, the model can easily be updated in the future to accommodate changes in CVD risk and risk factor levels in populations over time. If individual countries or even regions within a country have reliable data sources available, the model may even be recalibrated for even more precise risk estimations in that country or region. Because the same risk regions and data sources were used for systematic recalibration of SCORE2-OP as used in the SCORE2 project,[18] these two models can be used next to each other with persons naturally progressing from the SCORE2 model to SCORE2-OP as they get older.

Finally, the model can be used to estimate the absolute CVD risk reduction from blood pressure and cholesterol-lowering to blood pressure and LDL-cholesterol treatment goals, by applying the HRs from meta-analyses or clinical trials in older persons to the SCORE2-OP risk estimations. Higher levels of non-HDL-c confer a smaller increase in CV risk in older persons compared to young and middle-aged people. It should be noted that lowering cholesterol produces significant reductions in major vascular events

irrespective of age, although there is still less direct evidence of benefit among people older than 75 years without a history of previous vascular disease.[42] In general older persons are at high 10-year CVD risk as age is a major driver of risk. For older persons there are currently no CVD risk threshold for initiating risk factor lowering treatment in international guidelines. Should those thresholds appear, these may differ according to age as both the potential harms and the gain in CVD-free life expectancy from preventive therapy heavily depend on age. National and international guidelines need to consider (different) treatment thresholds for young, middle-aged and older persons. For example, the Norwegian guideline for primary prevention of CVD has a graded recommendation for consideration of intervention with pharmacological risk factor management (10-year CV risk over 5% in ages 45 - 54 years, over 10% in ages 55 - 64 years and over 15% in ages 65 - 74 years).[43] Using the SCORE2-OP model, no uncertainty regarding individual predictions was estimated. 10-year risk of CVD events can already be hard to interpret in clinical practice and having to interpret confidence intervals as well might make risk communication even more difficult, rather than more informed. Clinicians who want to incorporate the uncertainty of treatment decisions could consider adding the confidence intervals from meta-analyses or trials in the calculation of the ARR.

Estimation of absolute benefit may therefore guide treatment decisions in a shared decision making process taking frailty, biological age and patient preferences into account. Although on average the CVD risk is high in older persons, the current study shows that there is a wide distribution in 10-year CVD event risk in older persons, and that risk factor treatment does not necessarily yield a clinically significant benefit in all older persons. Therefore, in the future it might be interest to focus more on lifetime benefit from risk factor treatment based on lifetime CVD risk calculators.[44–46]

Several potential limitations of the current study should also be considered. First, the model was developed in a cohort study from the low-risk region alone. As such, the assumption is made that the model coefficients are transferrable to other risk regions. Previous studies have indeed shown homogeneity of model coefficients across different geographical regions and also across time for a CVD risk model, indicating transferability of model coefficients across different populations.[18,28] Results from the current study have shown that discrimination was adequate in all countries where external validation

was performed, indicating transferability of model coefficients was valid, although this validation could not be performed in all risk regions due to lack of adequate data. Ideally, the SCORE2-OP algorithm should be validated in those regions as soon as reliable data are available in these regions.

Second, for the systematic recalibration approach estimated total CVD event incidence rates rather than observed CVD event incidence rates were used within the four risk regions by using a multiplier-based approach. This approach is based on the assumption that the multipliers are valid across all countries within the same risk region. Previous studies have shown that the multipliers showed good consistency across both different cohorts from the same region and across time.[18] As such, we believe that this assumption is sufficiently met to give reliable estimations of total CVD event risk after systematic recalibration.

Third, part of the European validation data consisted of trial populations rather than unselected cohort data. Whereas the discrimination in our cohort populations was acceptable, especially compared to discrimination of a general risk model (namely ASCVD) in the same populations, slightly lower C-indices were reported in the external validation in the trial populations. Trial populations often make up a much more selected proportion of the population at large in comparison to cohort data (e.g. HYVET only contains patients aged 80 or older, with SBP ranging from 156 to 200 mmHg) and the maximum C-index is strongly associated to the distribution of risk within a study population.[40] Therefore, it is likely that the discrimination in these trials is an underestimation of the discrimination in real-life populations. As regional calibration (i.e. goodness of fit of the model) is satisfactory for all risk regions, the model can be used reliably for risk communication and treatment decisions in older persons.

Fourth, during model derivation in CONOR, no adjustment was made for treatment of risk factors at baseline. The assumption is made that, for example for cholesterol or blood pressure levels, the *current* risk factor level is predictive of the 10-year risk, regardless of whether this is treated or untreated. SCORE2-OP can thus be used for estimating 10-year risk in both untreated and treated individuals. However, caution should be given when risk factor treatment has been recently initiated. However, SCORE2-OP can be used for making treatment decisions in persons on a stable treatment regimen. Together with the fact that only one baseline risk factor measurement was used, which means that there may be underestimation of risk associations due to “regression dilution”,[47,48] this may contribute to the

relatively low discrimination. Additionally, no adjustment was made for the potential initiation of risk factor treatment during study follow-up, which may also influence discrimination. However, it has been shown that accounting for statin drop-in during follow-up in model development had only a limited impact on model performance.[49]

Fifth, predictors related to co-morbidity or frailty (e.g. kidney function, height and body weight, co-morbidity at baseline) may be important determinants for CVD risk in older persons, but were not included in SCORE2-OP due to the availability in the data sources. Including the number of drugs used as a measure of co-morbidity added to the predictive accuracy in the PROSPER older person score,[25] but this variable was not available in all relevant data sources.

Finally, an inherent limitation of absolute risk estimations, is that older individuals are invariably at higher risk for CVD than younger individuals with the same risk factors. As higher CVD risk translates to higher absolute risk reductions, this may give the impression that risk factors such as blood pressure and LDL-cholesterol should always be treated in the very old. It should be noted that 5- or 10-year CVD risk estimation should be combined with some assessment of treatment benefit, as life expectancy could be limited, together with patient preferences to make individual treatment decisions. For this purpose, lifetime treatment benefit approaches could be used, such as the LIFE-CVD model for primary prevention.[44]

In conclusion, the competing risk adjusted SCORE2-OP model to estimate 5- and 10-year CVD event risk in persons aged over 65 years was derived, recalibrated, and externally validated in four risk regions. These models can be used for communicating the risk of CVD events and potential benefits from risk factor treatment, and may facilitate shared decision making in CVD risk management in older persons.

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Disclosures:

Conflicts of interest

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Tables

Table 1: Study and baseline patient characteristics of the included study populations

	Derivation population	**External validation and testing populations**					
	CONOR	**ARIC**	**CPRD**	**HYVET**	**MESA**	**PROSPER**	**SPRINT**
	N = 28,503	N=5,153	N=319,390	N =3,381	N =2,977	N =3,254	N =4460
Recruitment period	1994-2003	2011-2013	2006*	2001-2007	2000-2002	1997-1999	2010-2013
Country	Norway	USA	UK	Eastern Europe (n=1895), Western Europe (n=84), other (n=1402)	USA	UK (n=1288), Ireland (n=1339), Netherlands (n=627)	USA
Baseline characteristics:							
Male sex	50%	39%	42%	38%	48%	42%	59%
Age (years)	73 ± 5	75 ± 5	74 ± 6	83 ± 3	72 ± 5	75 ± 3	74 ± 6
Current smoking	20%	7%	25%	7%	8%	33%	5%
SBP (mmHg)	152 ± 23	130 ± 18	141 ± 16	173 ± 9	134 ± 22	157 ± 21	141 ± 15
Total cholesterol (mmol/L)	6.4 ± 1.2	4.8 ± 1.1	5.5 ± 1.2	5.3 ± 1.1	5.0 ± 0.9	5.7 ± 0.9	4.9 ± 1.0
HDL-cholesterol (mmol/L)	1.5 ± 0.4	1.4 ± 0.4	1.6 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.4 ± 0.4
Type 2 diabetes mellitus	6%	31%	10%	9%	15%	12%	0%
Lipid-lowering drugs use	9%	49%	21%	0.3%	22%	49%	44%
Median follow-up (IQI)	13 (8-15)	6 (5-6)	7 (4-10)	2 (1-3)	13 (9-14)	3 (3-4)	3 (3-tab4)
Primary endpoint	10,089 (35%)	427 (8%)	31,484 (10%)	225 (7%)	501 (17%)	396 (12%)	186 (4%)
Total mortality	16,642 (58%)	683 (13%)	60,077 (19%)	356 (11%)	981 (33%)	274 (8%)	194 (4%)

All data in n (%) or mean ± standard deviation unless stated otherwise

* Baseline for measurement of exposure was set at 1/1/2006

SBP = systolic blood pressure; HDL = high-density lipoprotein; IQR = interquartile interval; UK = United Kingdom; USA = United States of America

Table 2: Sex-specific coefficients and subdistribution hazard ratios for CVD events of SCORE2-OP

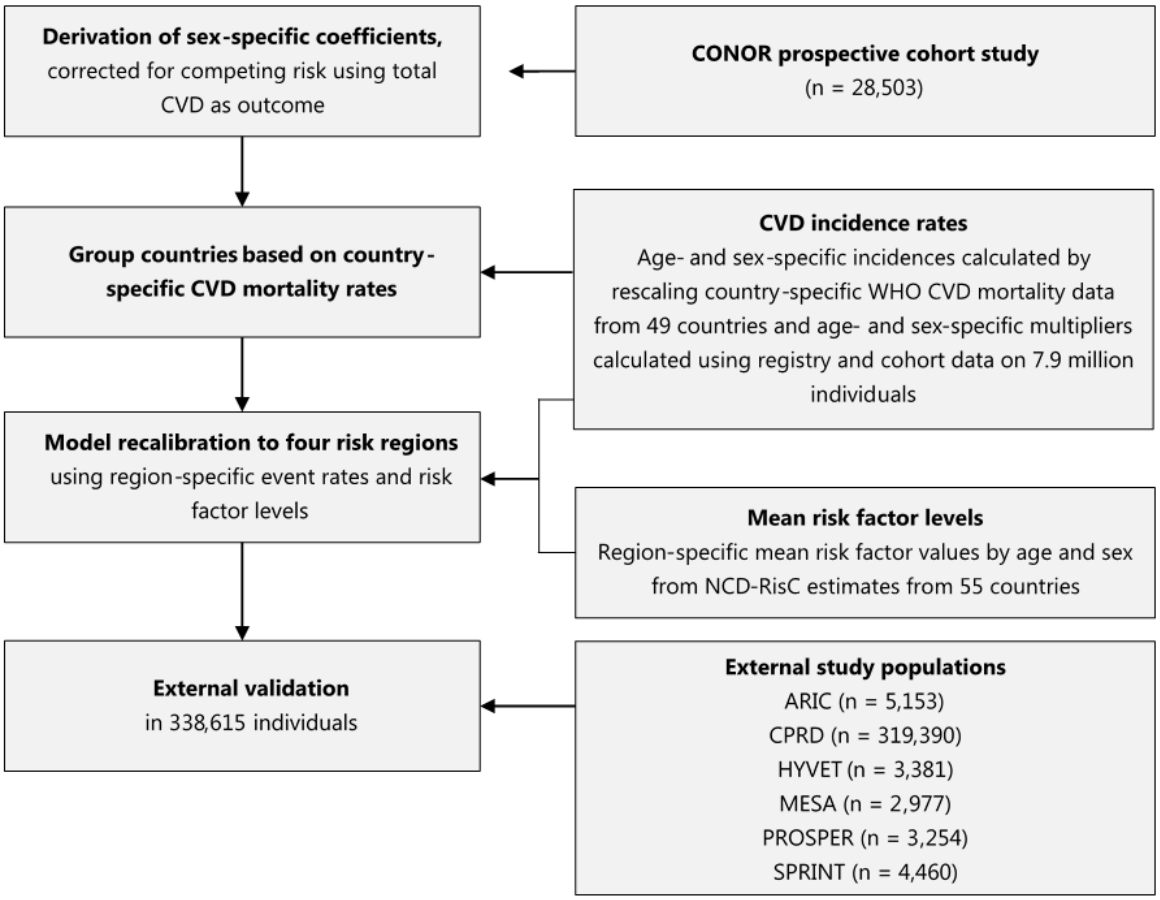
	Men		Women	
	Coefficients (95% CI)	Subdistribution hazard ratios	Coefficients (95% CI)	Subdistribution hazard ratios
Age (per year)	0.063 (0.055-0.071)	1.07	0.079 (0.070-0.087)	1.08
History of diabetes	0.425 (0.305-0.544)	1.50	0.601 (0.465-0.737)	1.80
History of diabetes * age (per year)	-0.017 (-0.040-0.005)		-0.011 (-0.032-0.011)	
Current smoking	0.352 (0.279-0.426)	1.39	0.492 (0.398-0.587)	1.59
Current smoking * age (per year)	-0.025 (-0.040- -0.009)		-0.026 (-0.043- -0.008)	
SBP (per 10 mmHg)	0.094 (0.079-0.109)	1.09	0.102 (0.085-0.119)	1.10
SBP (per 10 mmHg) * age (per year)	-0.005 (-0.008- -0.002)		-0.004 (-0.007- -0.002)	
Total cholesterol (per 1 mmol/L)	0.085 (0.054-0.116)	1.10	0.060 (0.027-0.094)	1.06
Total cholesterol (per 1mmol/L) * age (per year)	0.007 (0.002-0.013)		-0.001 (-0.056-0.004)	
HDL cholesterol (per 1 mmol/L)	-0.356 (-0.445- -0.268)	0.71	-0.304 (-0.403- -0.205)	0.75
HDL cholesterol (per 1 mmol/L) * age (per year)	0.009 (-0.009-0.027)		0.015 (0.0002-0.031)	

95% CI = 95% confidence interval

Sex-specific coefficients and subdistribution hazard ratios (SHRs) from Fine and Gray models predicted the risk of fatal and non-fatal CVD events as derived in the CONOR study. The SHRs are shown for age centred at 73 years, systolic blood pressure at 150 mmHg, total cholesterol at 6 mmol/L, and HDL cholesterol at 1.4 mmol/L.

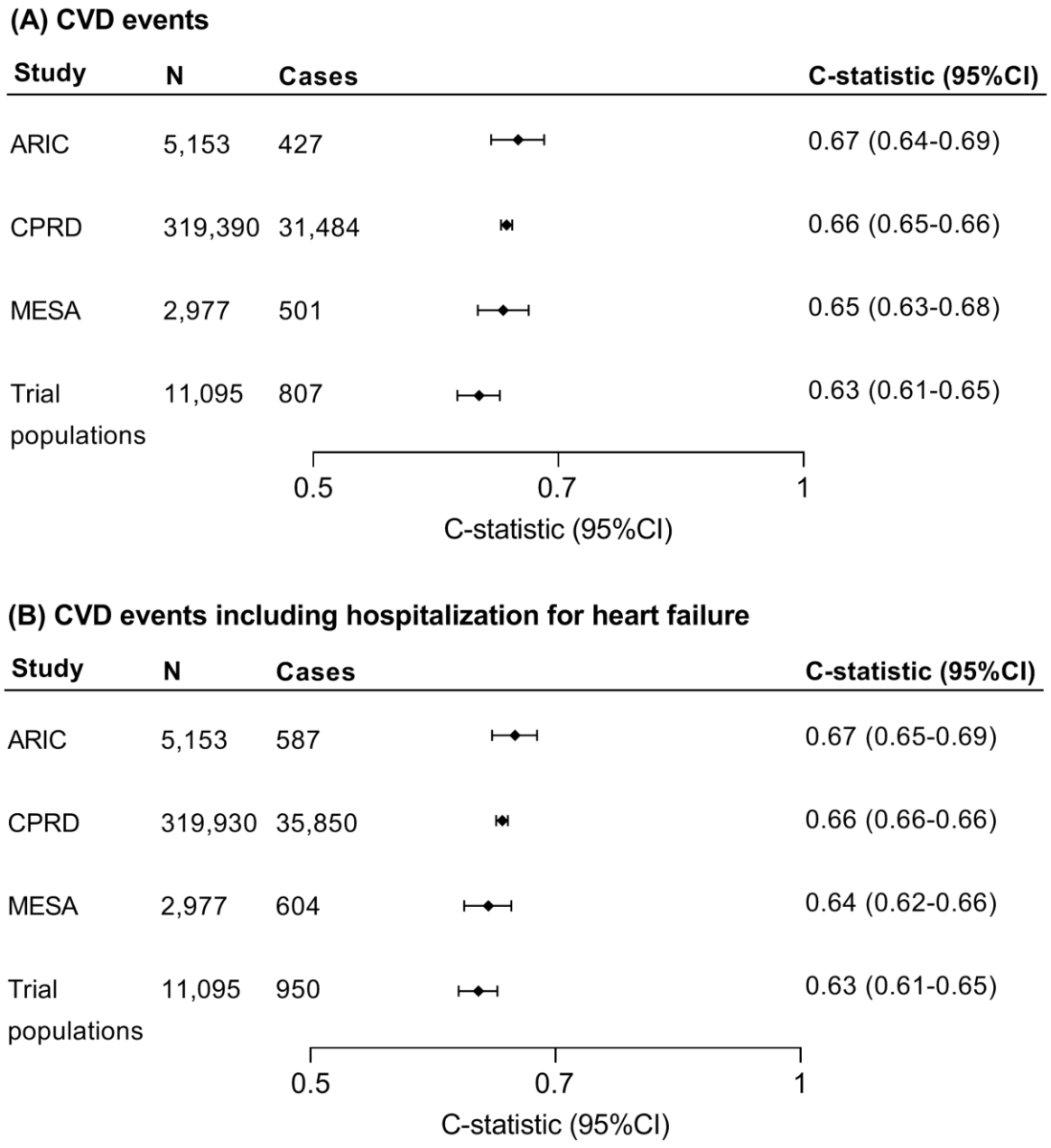
These SHRs are relevant for risk estimation only and have no etiological interpretation.

Figure 1: Study design



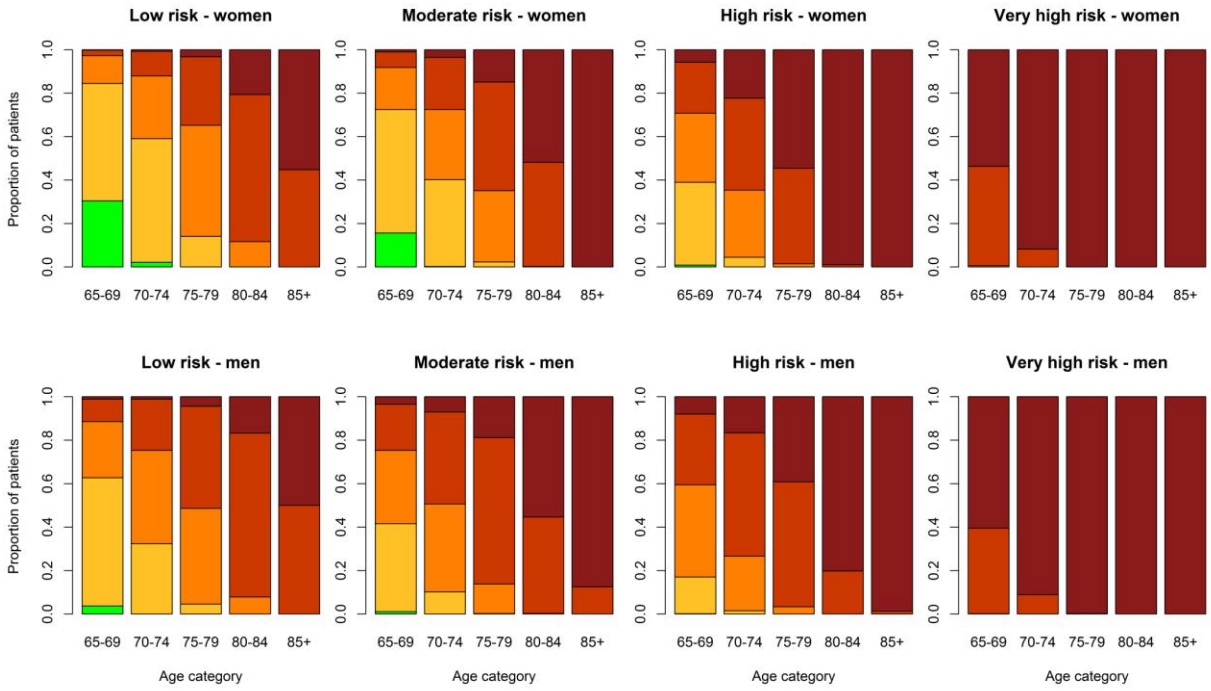
Abbreviations: ARIC = Atherosclerosis Risk in Communities; CONOR = Cohort of Norway; CPRD = Clinical Practice Research Datalink; CVD = cardiovascular disease; MESA = Multi-Ethnic Study of Atherosclerosis; NCD-RisC = non-Communicable Disease Risk Factor Collaboration; PROSPER = PROspective Study of Pravastatin in Elderly at Risk; SPRINT = Systolic Blood Pressure Intervention Trial; WHO = World Health Organisation

Figure 2: External validation of SCORE2-OP for (A) the estimation of risk for myocardial infarction (MI), stroke, or CVD mortality (primary endpoint); (B) the estimation of risk for MI , stroke, hospitalization for heart failure, or CVD mortality (CVD events including heart failure)



Trial populations: HYVET, PROSPER and SPRINT

Figure 3: Age- and sex-specific distributions of fatal and non-fatal CVD risk in the four risk regions according to SCORE2-OP.



Age- and sex-specific risk distribution in the different risk regions, based on risk factor data in ARIC and MESA cohorts (n = 8,130).

Figure 4: Distribution of estimated 10-year fatal and non-fatal CVD events and estimated 10-year absolute risk reduction (ARR) from blood-pressure lowering in older persons with hypertension (SBP >140 mmHg) in the HYVET and SPRINT trials (n = 5,579).

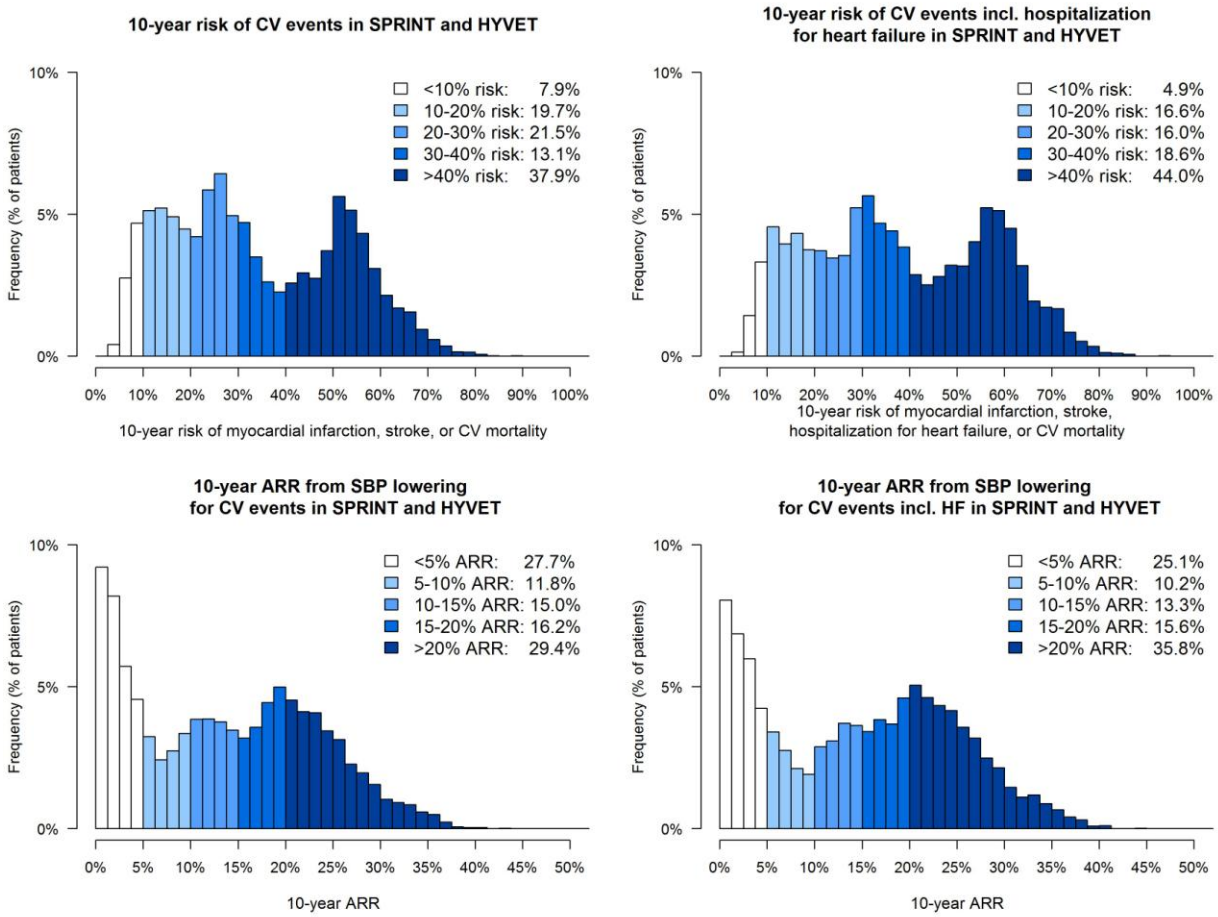
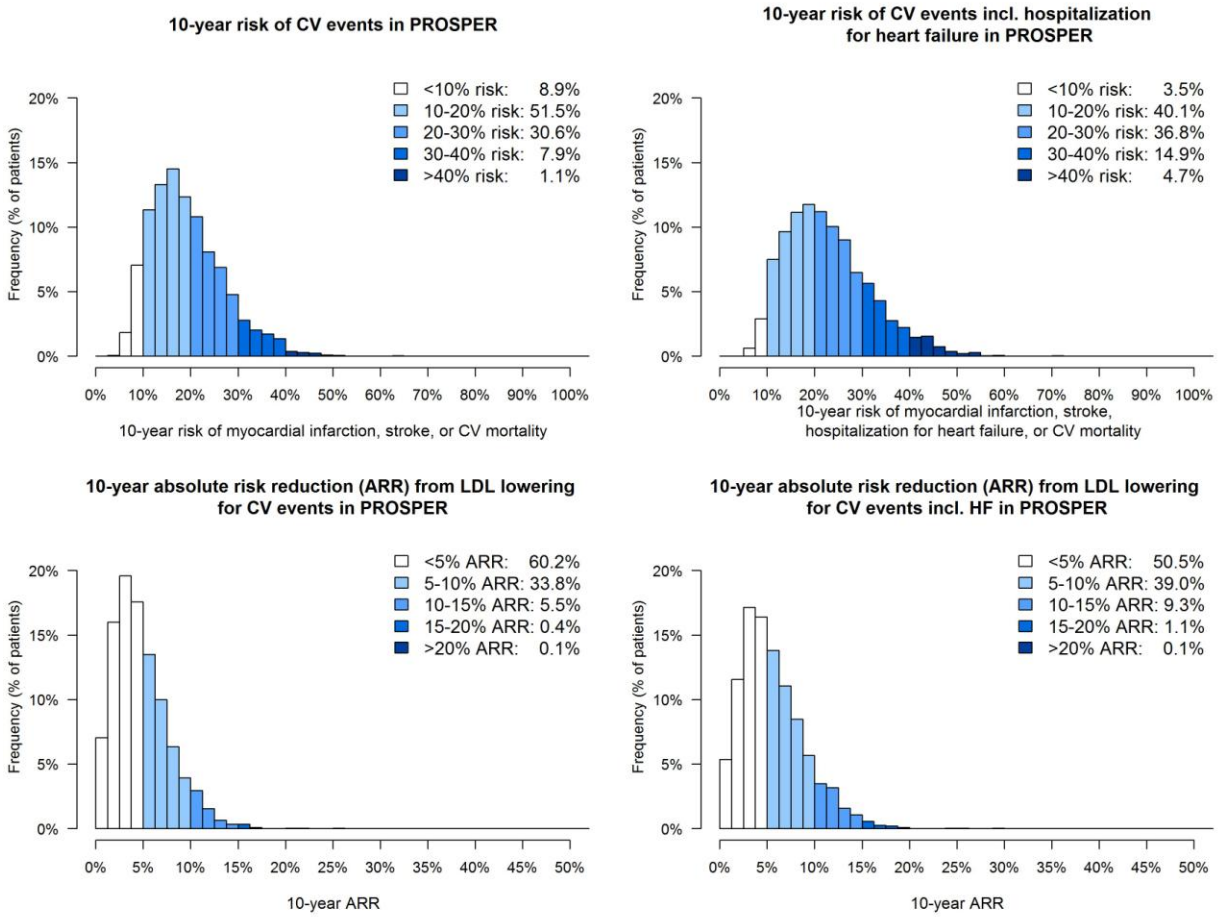


Figure 5: Distribution of estimated 10-year non-fatal and fatal CVD events and estimated 10-year absolute risk reduction from lipid lowering in older persons with cholesterol >2.6 mmol/L in the PROSPER trial (n = 3,051).



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