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FULL RESEARCH PAPER
Risk Prediction/Assessment & Stratification

Prediction of recurrent event in patients with coronary heart disease: the EUROASPIRE Risk Model

Results from a prospective study in 27 countries in the WHO European region - The EURObservational Research Programme (EORP) of the European Society of Cardiology (ESC)

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Aims Most patients with established atherosclerotic cardiovascular disease (CVD) are at very high risk for developing recurrent events. Since this risk varies a lot between patients there is a need to identify those in whom an even more intensive secondary prevention strategy should be envisaged. Using data from the EUROASPIRE IV and V cohorts of coronary heart disease (CHD) patients from 27 European countries, we aimed at developing and internally and externally validating a risk model predicting recurrent CVD events in patients aged < 75 years.

Methods and results Prospective data were available for 12 484 patients after a median follow-up time of 1.7 years. The primary endpoint, a composite of fatal CVD or new hospitalizations for non-fatal myocardial infarction (MI), stroke, heart failure, coronary artery bypass graft, or percutaneous coronary intervention (PCI), occurred in 1424 patients. The model was developed based on data from 8000 randomly selected patients in whom the association between potential risk factors and the incidence of the primary endpoint was investigated. This model was then validated in the remaining 4484 patients. The final multivariate model revealed a higher risk for the primary endpoint with increasing age, a previous hospitalization for stroke, heart failure or PCI, a previous diagnosis of peripheral artery disease, self-reported diabetes and its glycaemic control, higher non-high-density lipoprotein cholesterol, reduced

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renal function, symptoms of depression and anxiety and living in a higher risk country. The model demonstrated excellent internal validity and proved very adequate in the validation cohort. Regarding external validity, the model demonstrated good discriminative ability in 20 148 MI patients participating in the SWEDEHEART register. Finally, we developed a risk calculator to estimate risks at 1 and 2 years for patients with stable CHD.

Conclusion In patients with CHD, fatal and non-fatal rates of recurrent CVD events are high. However, there are still opportunities to optimize their management in order to prevent further disease or death. The EUROASPIRE Risk Calculator may be of help to reach this goal.

Keywords Coronary heart disease • Risk • Patient management • Recurrent events

Introduction

A large proportion of all cardiovascular events occur in patients with established cardiovascular disease (CVD).[1] According to European and US prevention guidelines, patients with clinically manifest CVD are considered to be at high or very high risk for recurrent events and should therefore be given the highest priority in clinical practice.[2,3] Prognosis in patients with existing CVD is predominantly associated with the severity of the underlying coronary artery disease, functional left ventricular impairment and associated comorbidities such as heart failure, stroke, peripheral artery disease (PAD), diabetes, and renal insufficiency. By addressing lifestyle, risk factor control and adherence with cardioprotective medications, the risk of subsequent cardiovascular events can be reduced and life expectancy improved through comprehensive prevention programmes.[4] However, the EUROASPIRE (EUROpean Action on Secondary Prevention through Intervention to Reduce Events) surveys have repeatedly demonstrated that the management of patients with documented coronary heart disease (CHD) falls short of the standards set by the European Guidelines on CVD Prevention in Clinical Practice and there is substantial potential for improvement.[5] Although CHD patients most often share a common causal pathway, their response and adherence to treatment may be very different. For instance, the response in low-density lipoprotein (LDL) cholesterol to a given statin or PCSK9 inhibitor shows considerable inter-individual variation.[6,7]

Unfortunately, as in primary care, a great deal of emphasis in secondary care is still being placed on the management of individual risk factors rather than adopting a multifactorial treatment strategy accounting for the fact that risk factors may exert an accumulative effect . Despite the availability of a few risk assessment models such as those developed in the SMART (Secondary Manifestations of Arterial Disease study) and REACH (REduction of Atherothrombosis for Continued Health) studies, the concept of absolute risk to identify patients who may benefit from more aggressive lifestyle interventions and pharmacological therapy on top of recommended evidence-based treatments, is not yet widely implemented in secondary care.[8,9]

The purpose of this study was to complement secondary care by developing a new robust risk model for predicting short-term recurrent fatal and non-fatal cardiovascular events based on a set of independent risk factors and using data from a large European-wide contemporary study mirroring real-world clinical practice.

Methods

Patients and data collection

The EUROASPIRE study (European Action on Secondary and Primary Prevention by Intervention to Reduce Events, and later referred to as the European Survey of CVD Prevention and Diabetes) is a series of five large cross-sectional surveys in patients with documented CHD undertaken since 1995 in several countries that adopted the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice issued by the European Society of Cardiology.[2,5] The aim was to generate an objective assessment of the implementation of these guidelines in CHD patients by describing their management through lifestyle modifications and use of drug therapies. In the last two surveys, EUROASPIRE IV (24 countries, 2012–13) and EUROASPIRE V (27 countries 2016–17), patients were also followed prospectively for incident fatal and non-fatal cardiovascular events.

A detailed description of these last two surveys has been published elsewhere.[5,10] In summary, consecutive female and male CHD patients from geographical areas within the participating countries were identified from hospital discharge lists or diagnostic registers and invited to participate in the study by attending an interview and medical examination. At least 6 months but not more than 3 years prior to this baseline visit, all patients had been hospitalized for a first or recurrent diagnosis of an acute myocardial infarction (MI) or acute myocardial ischaemia, or for treatment with elective or emergency coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). In EUROASPIRE IV and V respectively 6937 and 6507 coronary patients aged < 75 years from hospitals and cardiac centres in 29 different countries, attended the study visit. We aimed at developing a risk model for countries belonging to the WHO European region, hence 348 EUROASPIRE V patients from Egypt were excluded. The average time between the hospital admission for the recruiting event or procedure and the study visit was about 16 months. The visit consisted of an interview, filling out a number of questionnaires and a medical examination including anthropometric measurements, blood pressure recording, an assessment of carbon monoxide in breath to validate self-reported smoking habits and sampling of fasting venous blood for the biochemical measurements. All these data were collected by centrally trained research staff according to standardized methods including the use of the same devices in all centres and a central laboratory for all venous blood analyses (Biochemistry Laboratory at the National Institute for Health and Welfare, Helsinki).

Potential risk factors

A low educational level was defined as primary school level only or less. A patient was labelled as a smoker if he/she reported being a current smoker or had an exhaled carbon monoxide level exceeding 10 ppm recorded by a Smokerlyzer (Bedfont Scientific, Model Micro+). Waist

circumference was recorded using a metal tape measure at the level midway between the lower rib margin and the iliac crest at the end of a normal expiration. Regular physical activity was defined as 'performing physical activity for at least 30 min on average, five times a week'. Reduction of fat and alcohol intake and increase of the consumption of fruit and vegetables were defined as a positive answer to the specific question, posed at interview, whether or not the patient had changed diet since the hospital discharge for the recruiting event. Participation in a cardiac prevention and rehabilitation programme was defined as attending at least half of the prescribed sessions within 3 months following hospital discharge for the recruiting event or procedure. Patients were considered to be adherent to their drug therapies if they reported taking their prescribed drugs at least 90% of the time. Blood pressure was measured twice in the sitting position on the right arm using an automatic digital sphygmomanometer (OMRON Corporation, Kyoto, Japan). Venous blood was drawn for determination of serum total and high-density lipoprotein (HDL) cholesterol, triglycerides, serum creatinine, and glycated haemoglobin A1c (HbA1c). LDL cholesterol was calculated using Friedewald's formula; non-HDL cholesterol was the difference between total and HDL cholesterol. Controlled diabetes was defined as HbA1c <7% in patients with known diabetes. The glomerular filtration rate (eGFR) was estimated from serum creatinine by means of the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI).[11] Symptoms of anxiety and depression were assessed through the Hospital Anxiety and Depression Scale (HADS) instrument in cardiac patients.[12] For each scale, scores vary between 0 and 21 with higher scores indicating more severe symptoms. Scores <8 can be considered as being in the normal range, higher scores can indicate mild (scores 8–10) or more severe symptoms (scores ≥ 11).

Follow-up and primary endpoint

Follow-up information was gathered from patients themselves, medical records, mortality registers, other external registries, municipal records and archives or by contacting the patients' family or family doctor. The collected information comprised vital status, date and cause of death ('coronary heart disease', 'stroke', 'other vascular', 'cancer', or 'other causes') as well as new hospitalizations for CVD following the date of the baseline interview. The primary cardiovascular outcome was defined as the first of cardiovascular death or hospitalization for non-fatal MI, stroke, heart failure, CABG or PCI. In case of several non-fatal events, only the first occurring was included in our analyses. Time at risk for developing the primary endpoint was calculated as the time between the study visit and the date of death or the date of the first hospitalization for a non-fatal cardiovascular event or procedure. In case no primary event had occurred, time at risk was censored at the date of ending the follow-up with a minimum of 1 year after the baseline visit. To ensure qualitative follow-up information, data from Kazakhstan were not included because they did not reach the a priori decided threshold of 75% completeness.

Statistical methods

Anticipating a cumulative incidence of the primary outcome of 15% at 2 years, sample size calculations revealed that for estimating minimal detectable hazard ratios of 1.5 at the $\alpha = 0.05$ significance level, the combined sample of EUROASPIRE IV and V patients was sufficiently large to result in 90% statistical power. Distributions of baseline characteristics were summarized using means, standard deviations and proportions. Incidence rates were standardized for age according to the direct method with the age distribution of the complete sample as reference. Event-free survival curves for the three country risk groups separately were constructed according to the Kaplan–Meier product-limit method (*Figure 1*). In our analyses, we chose to fit a parametric model for the event-free survival times as these models do not require the assumption of proportionality of hazards. Because log(-log(S(t))) proved linearly related to log(t), where S(t) is the Kaplan–Meier survival estimate, the Weibull model emerged as giving the best fit to our survival data.

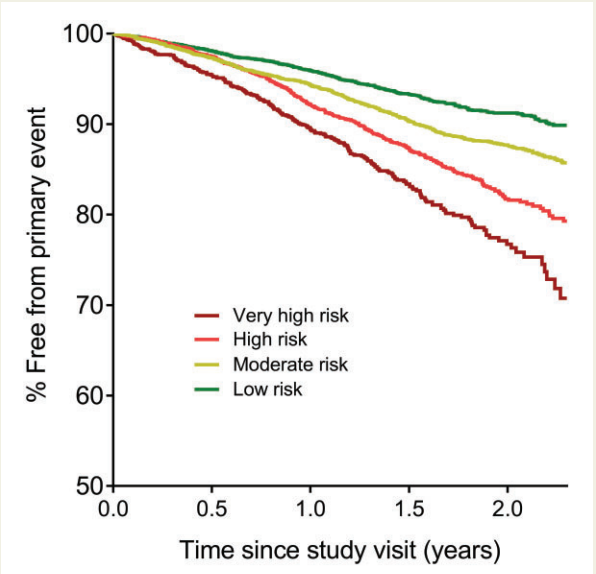

Figure 1 Cardiovascular event-free survival in coronary heart disease patients according to the countries' risk level.

Prior to any modelling, we chose to apply a split-sample technique to develop and validate the final model. We randomly selected 8000 patients from the entire sample for deriving the model ('derivation cohort') and used the remaining sample of 4484 patients for validating the model ('validation cohort'). The model in the derivation cohort was developed in two steps. First, we looked at associations between potential risk factors (listed in *Table 2*) and the incidence of the primary endpoint in the derivation cohort through fitting Weibull models for each risk factor individually with adjustment for age and country. The strengths of these associations were expressed as hazard ratios with 95% confidence intervals (CI). Risk factors which in these separate Weibull models were found to be significantly related to the endpoint at the $\alpha = 0.10$ significance level, were then entered in a single multivariate Weibull model. The latter model was then subjected to a backward elimination procedure for sequentially removing variables in order to end up with a parsimonious model. An α-level of 0.05 was used as significance threshold for keeping variables in the final model. In our analyses, eGFR values were log-transformed because of a high degree of skewness. By adding polynomial terms for the continuous variables to the model and evaluating subsequent changes in log-likelihood statistics, we detected no strong deviations from linearity apart from a clear curvilinear relation between LDL cholesterol and the incidence of the primary endpoint. Interactions between risk factors were assessed by evaluating the significance of their cross-products in the model. As only a relatively small number of 79 non-cardiovascular deaths occurred in this large sample of over 12 000 CHD patients < 75 years and the large majority of primary endpoints were non-fatal, we did not correct the model for competing risks. Our cohort data were quite complete with missing information only exceeding one percent on the anxiety and depression scores (4%), the dietary variables (2%), and on the physical activity item (1%). Nevertheless, in deriving a parsimonious model, we used multiple imputation using the SAS procedure PROC MI to replace missing values by a chained equations method.[12]

We created 25 imputed datasets and fitted the Weibull models in each of these datasets. Point estimates and variances were then combined across all datasets by applying Rubin's rule to obtain final model estimates (SAS procedure PROC MIANALYZE).[13]

Model performance within each cohort was assessed by discrimination (the model's ability to discriminate between patients with or without the primary endpoint) and calibration (the model's ability to quantify the observed absolute risk). For discrimination, we reported Uno's concordance C-statistics which estimate for two randomly chosen subjects, the probability that the model predicts a higher risk for the subject with the poorer outcome.[14] Calibration performance was assessed by visually inspecting a calibration plot and by evaluating the agreement between observed and predicted risk across the full range (deciles) of predicted risk using the Hosmer–Lemeshow χ^2 statistic (8 degrees of freedom) with *P*-values above 0.10 indicating a good model fit. Observed risks at 2 years were calculated according to the Kaplan–Meier method. Overall, a type I error level of $\alpha = 0.05$ was used to indicate statistical significance. All data analyses were undertaken using SAS statistical software (release 9.4) in the Department of Public Health and Primary Care, Ghent University, Belgium.

External validation

We validated our model externally using data from the SWEDEHEART register (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies).[15] All patients in Sweden admitted with an MI to a coronary care unit or other specialized in-patient facility are continuously included in this register. During the period 2012–16, 25 581 patients aged <75 years participated in the SWEDEHEART secondary prevention follow-up programme including a follow-up visit at 12–14 months after their MI. After exclusion of patients with missing data on eGFR, non-HDL cholesterol or HbA1c, 20 148 patients were available to externally validate our risk model. Since no data on anxiety and depression were recorded in SWEDEHEART, the mean Swedish HADS scores as observed in our study were imputed. In this external validation, the same composite endpoint was used: fatal CVD or non-fatal MI, stroke, heart failure, CABG, or PCI in the period up to 2 years after the follow-up visit.

Data management

All data management was undertaken by the EURObservational Research Programme Department of the European Society of Cardiology according to the requirements defined by the appointed Executive Committee with the support of the EURObservational Research Programme (EORP) Team. The database is located in the European Heart House, Sophia-Antipolis, France. All data were collected electronically using web based data entry. Names were not sent to the data management centre where information is held on each subject using a unique identification number for country, centre and individual. Data were updated electronically by each country and submitted via the internet to the data management centre where checks for completeness, internal consistency and accuracy were run. All data are stored under the provisions of the National Data Protection Regulations.

Ethical procedures

National Coordinators were responsible for obtaining Local Ethics Committees approvals. Written, informed consent was obtained from each participant and stored in the patient file. The research assistants signed the Case Record Form to confirm that informed consent was obtained and stored the original signed declaration consent in the patient's file.

Results

In total, baseline data obtained at the study visit were available in 13 452 patients. We had access to follow-up data in 12 763 of them (95%). Among these, 279 (2%) patients were excluded because of insufficient data on non-fatal events, defined as missing information during follow-up on at least three of the following hospitalized events: PCI, CABG, acute myocardial infarction, stroke, or heart failure. Hence, valid information on the occurrence of the primary endpoint (fatal or non-fatal cardiovascular events) was available in 12 484 patients. Follow-up data were obtained from the patients themselves in 60% of cases, abstracted from hospital records in 28%, through contacting the family doctor in 2% and by any other method of data collection in 10% of patients. Median (P25–P75) follow-up time was 1.7 (1.3–2.0) years. During this period, 188 fatal events were recorded; 109 deaths (58%) were due to CVD, 49 due to cancer, and 30 due to any other cause. Regarding the incidence of non-fatal events, 250 patients were hospitalized for an acute MI, 175 patients for stroke, 377 for heart failure, 685 for PCI, and 93 for CABG. The primary endpoint occurred in 1424 patients giving an incidence rate of 71 per 1000 person-years. The number of patients at baseline as well as the age-standardized incidence rates of the primary endpoint by country, gender and age, are shown in *Table 1*. The observed primary event rate was slightly higher in women, although this difference dropped after age-adjustment. The age-adjusted hazard ratio (95% CI) for the primary endpoint in women versus men was 1.08 (0.98–1.20), $P = 0.12$. Variation of primary event rates in the age range 45–64 years was rather minimal; this pattern was seen in both men and women.

Given the large variability in incidence between countries we pooled them in four risk categories based on the incidence of the composite of fatal CVD, non-fatal MI, stroke, or heart failure with inclusion of surgical procedures. For very high risk countries, the age-standardized incidence of this primary endpoint was >100 per 1000 person-years (Bulgaria, Greece, Kyrgyzstan, Latvia, Turkey; including 1472 patients), high-risk countries were those with an age-standardized incidence between 80 and 100 per 1000 person-years (Lithuania, Russian Federation, Serbia, Ukraine; including 2514 patients); countries were at moderate risk if the age-standardized incidence of the primary endpoint was between 60 and 80 per 1000 person-years (Bosnia and Herzegovina, Croatia, Cyprus, France, Germany, Poland, Romania; including 4335 patients) and at low risk if the age-standardized incidence of the primary endpoint was <60 per 1000 person-years (Belgium, Czech Republic, Finland, Ireland, Italy, Netherlands, Portugal, Slovenia, Spain, Sweden, United Kingdom; including 4163 patients). *Figure 1* depicts the event free survival curves (Kaplan–Meier method) in these four risk groups of countries.

Baseline characteristics of the derivation and validation cohorts are shown in *Table 2*. As expected, the distributions of these characteristics in both cohorts are very similar. The incidence of the primary endpoint was 70.7/1000 person-years in the derivation cohort and 70.9/1000 person-years in the validation cohort ($P = 0.94$). Expressed as hazard ratios derived from individual Weibull models with adjustment for age and country, the associations between risk factors separately and the incidence of fatal and non-fatal cardiovascular events in the derivation sample are presented in *Table 3*. These analyses indicated that the primary endpoint was not significantly

Table 1 Number of patients and incidence of fatal and non-fatal cardiovascular events

	N	Person-years of observation	Fatal and non-fatal cardiovascular events	
			Number of events	Incidence rate[a]
Belgium	448	652	31	48
Bosnia and Herzegovina	442	676	43	61
Bulgaria	403	506	55	108
Croatia	744	1126	86	77
Cyprus	43	81	6	73
Czech Republic	744	1120	71	60
Finland	518	1059	61	57
France	334	681	43	63
Germany	571	904	76	79
Greece	120	148	15	103
Ireland	447	820	21	25
Italy	128	153	4	19
Kyrgyzstan	290	394	47	112
Latvia	301	524	78	146
Lithuania	709	1146	95	84
Netherlands	572	1118	63	57
Poland	650	1125	68	62
Portugal	254	288	13	43
Romania	807	1484	88	62
Russian Federation	710	1150	115	100
Serbia	488	854	84	99
Slovenia	334	586	25	41
Spain	417	630	25	39
Sweden	510	848	31	35
Turkey	358	484	62	140
Ukraine	607	827	76	94
United Kingdom	535	744	42	58
Men	9568	15 441	1062	69
Women	2916	4687	362	76
Age < 45 years	463	765	30	39
Age 45–54 years	2120	3384	241	71
Age 55–64 years	4802	7807	523	67
Age 65–74 years	5099	8172	630	77
All	12 484	20 128	1424	71

[a]Age-standardized incidence rate per 1000 person-years.

associated at the $\alpha = 0.10$ level with gender, time since hospital discharge for the recruiting event, educational level, current or former smoking, reduced fat or alcohol intake, body mass index, previous hospitalization for CABG, the use of antiplatelets, blood pressure or lipid lowering lowering drugs, medication adherence, and measured blood pressure. The relation between LDL cholesterol and outcome was found to be signficantly curvilinear ($P < 0.0001$ for the quadratic term) in this age-adjusted analysis. The remaining variables were entered simultaneously in a multivariate Weibull model with additional adjustment for age and country and subjected to a backwards elimination procedure. The results of the latter analysis are given *Table 4*. The final multivariate model revealed that patients previously hospitalized for stroke, heart failure or PCI, having a history of PAD or diabetes, a higher non-HDL cholesterol, a lower eGFR, showing signs of anxiety or depression or those living in a higher country, were all at significantly and independently higher risk of developing the primary event. A significant interaction between levels of anxiety and age was observed with anxiety being more prognostic in younger patients. The curvilinear association between LDL cholesterol and the occurrence of the primary endpoint dropped. Although of borderline significance, the beneficial impact of having attended a cardiac prevention and rehabilitation programme was not retained in this model in the derivation cohort with a hazard ratio (95% CI) of 0.89 (0.78–1.02), $P = 0.083$. *Table 4* also depicts the results of fitting the same model in the complete sample.

Table 2 Baseline characteristics of the derivation and validation cohorts

	Derivation cohort (*N* = 8000)	Validation cohort (*N* = 4484)
Age at interview (years)	61.9 (8.4)[a]	61.8 (8.5)
Female	23% (1878)	23% (1038)
Time since recruiting event < 1 year	35% (2783)	35% (1590)
Low educational level	14% (1137)	15% (675)
Currently smoking	19% (1480)	18% (827)
Regular physical activity	39% (3116)	40% (1774)
Reduction of fat intake	76% (5961)	78% (3437)
Increased consumption of fruit and vegetables	75% (5879)	76% (3377)
Reduction of alcohol intake	54% (4217)	56% (2430)
Attended a cardiac rehabilitation programme	38% (3023)	38% (1702)
HADS anxiety score	5.39 (3.85)	5.40 (3.92)
<8	73% (5573)	73% (3119)
8–10	16% (1191)	15% (644)
≥11	11% (837)	12% (497)
HADS depression score	4.62 (3.64)	4.62 (3.72)
<8	78% (5924)	77% (3298)
8–10	15% (1128)	15% (628)
≥11	7% (549)	8% (334)
Body mass index (kg/m^2)	29.3 (4.8)	29.3 (4.8)
≥30 kg/m^2	39% (3120)	39% (1758)
Waist circumference (cm)	101.9 (12.4)	102.0 (12.6)
≥102/88 cm for men/women	59% (4686)	59% (2630)
Previous hospitalization for CABG	20% (1571)	20% (878)
Previous hospitalization for PCI	73% (5854)	74% (3306)
Previous hospitalization for stroke	5% (405)	5% (211)
Previous hospitalization for heart failure	7% (584)	7% (335)
Previous diagnosis of peripheral artery disease	4% (326)	5% (210)
Diabetes status		
No self-reported diabetes	73% (5804)	73% (3231)
Controlled diabetes	14% (1099)	14% (627)
Uncontrolled diabetes	13% (1029)	13% (578)
Aspirin or other anti-platelets	94% (7481)	94% (4212)
Blood pressure lowering drugs	96% (7596)	95% (4252)
Lipid-lowering drugs	87% (6899)	88% (3913)
Drug adherent	91% (7278)	91% (4087)
Systolic blood pressure (mmHg)	134.1 (18.7)	133.7 (18.6)
Diastolic blood pressure (mmHg)	80.1 (11.0)	79.9 (11.0)
SBP/DBP ≥ 140/90 mmHg[b]	40% (3214)	40% (1772)
Resting heart rate (b.p.m.)	67.4 (10.9)	67.3 (10.7)
60–74 b.p.m.	53% (4239)	54% (2420)
≥75 b.p.m.	23% (1805)	22% (985)
eGFR (mL/min/1.73 m^2)	84.4 (19.8)	84.6 (19.7)
45–59 mL/min/1.73 m^2	7% (588)	7% (321)
<45 mL/min/1.73 m^2	4% (282)	4% (156)
Total cholesterol (mmol/L)	4.34 (1.17)	4.31 (1.12)
≥4.5 mmol/L	37% (2942)	36% (1619)
LDL cholesterol (mmol/L)	2.43 (0.96)	2.41 (0.95)
1.8–2.4 mmol/L	36% (2840)	36% (1618)
≥2.5 mmol/L	39% (3080)	38% (1690)
Non-HDL cholesterol (mmol/L)	3.20 (1.13)	3.17 (1.07)
≥2.2 mmol/L	84% (6722)	84% (3767)

Continued

Table 2 *Continued*

	Derivation cohort (*N* = 8000)	Validation cohort (*N* = 4484)
Country of recruitment		
Low risk	33% (2662)	33% (1501)
Moderate risk	35% (2778)	35% (1557)
High risk	20% (1607)	20% (907)
Very high risk	12% (953)	12% (519)

[a]Cell entries are mean (SD) or % (*n*).
[b]≥140/85 mmHg in patients with diabetes.

Regarding internal validity of the model in the derivation sample, Uno's C-statistic (95% CI) was 0.67 (0.64–0.70) which indicates an adequate discriminative ability. In terms of calibration, the model performed well as can be seen in the calibration plot presented as *Figure 2A*. The good model fit was confirmed by the Hosmer–Lemeshow test statistic being $\chi^2 = 10.9$ for 8 degrees of freedom ($P = 0.21$). The same model proved very adequate in the validation cohort as well with good discrimination given a Uno's C-statistic (95% CI) of 0.69 (0.64–0.73). Regarding calibration, the model fit in the validation cohort was good with a Hosmer–Lemeshow test statistic of $\chi^2 = 5.9$ ($P = 0.66$). *Figure 2B* depicts the good match between observed and predicted 2 years probabilities of the primary event in the validation cohort.

The incidence of the primary endpoint in the external validation cohort of SWEDEHEART patients was exactly the same as observed in our Swedish patients (35 per 1000 person-years). Our risk model demonstrated good discriminative ability in SWEDEHEART with a C-statistic (95% CI) of 0.64 (0.63–0.66). Excluding revascularization from the outcome further increased the C-statistic (95% CI) to 0.68 (0.66–0.70).

Based on the data from the complete sample of 12 484 patients, we developed an online EUROASPIRE risk calculator for calculating 1 and 2-year risks of fatal and non-fatal cardiovascular events for stable CHD patients from low, moderate, high, and very high countries from the WHO European region. A preview of this EUROASPIRE risk calculator can be consulted on the webpage https://www.calconic.com/calculator-widgets/euroaspire-risk-factor-calculator/5f6223fab75b14001e1f3c67?layouts=true (Supplementary material online, *Figure S1*).

Discussion

We invited CHD patients for the study visit in a stabilized phase of their disease, at least 6 months following hospital discharge for the recruiting event or procedure. This time interval was considered sufficiently large to allow healthier lifestyles, effective risk factor management to targets and optimizing cardioprotective drug treatment including dose titration as required.

The subsequent incidence of fatal and non-fatal cardiovascular events demonstrated a substantial variation between countries reflecting differences in health care systems, availability of specialist care including interventional cardiology and cardiac surgery, cardioprotective drugs as well as patients' risk factor profiles and behaviour. Cardiovascular incidence rates were comparable between men and women. This is in agreement with data from the SMART study as well as from the large STABILITY trial and the REACH registry in which no gender-differences were found in prognosis following a coronary event.[8,16,17] A literature study presented conflicting evidence about differences in outcome between men and women.[18] Nevertheless, it remains still unclear whether gender can be considered as an independent risk factor, since in many studies gender differences disappeared after multivariate adjustment.

The lack of a predictive value of smoking and recommended dietary changes, even in univariate analysis, may indicate that the residual impact of lifestyle behaviour in CHD patients may be outweighed by chronic comorbidities reflecting the severity of the underlying disease and associated complications even in those <75 years old. In particular, the absence of an association between smoking at the baseline visit and subsequent cardiovascular events, is in line with data from the Framingham Heart Study in patients with existing CHD.[19] This may be partly due to the fact that about half of the patients who smoked before the recruiting event, quit smoking in the period between hospital discharge and the study visit of at least 6 months and at most 3 years later. This period may have been too short to reveal the longer-term impact of smoking cessation so that this relatively large group of former smokers still carried a similar risk to current smokers. However, it has to be stressed that across Europe, a quarter of CHD patients who were smoking prior to hospitalization had no intention to quit after the event. In our analyses, performing recommended levels of physical activity was associated with a borderline significant benefit for recurrent events after age-adjustment. However, in multivariate analysis, this protective effect disappeared when adjusting for other risk factors and comorbidities, a phenomenon often seen in prospective studies in CHD patients such as the KAROLA study.[20]

Our data are fully in line with the accumulating evidence that depression and anxiety are strong independent risk factors for the development of recurrent events in patients with acute coronary syndrome.[21,22] Interestingly, depressive feelings were associated with adverse outcome across the entire age span in our analyses, while feelings of anxiety were mainly related to outcome at younger ages, especially those under 50 years at the time of the study visit. Given the well-documented beneficial impact of psychological interventions in CHD patients, our data further indicate that psychological

Table 3 Associations between risk factors and the incidence of the primary endpoint in the derivation cohort

	Hazard ratio (95%)[a], *P*-value
Age	1.11 (1.04–1.19), *P* = 0.0020
Female	1.03 (0.91–1.17), *P* = 0.60
Time since recruiting event (per year)	0.94 (0.86–1.03), *P* = 0.21
Low educational level (vs. higher)	1.12 (0.96–1.30), *P* = 0.16
Currently smoking (vs. no)	0.89 (0.77–1.04), *P* = 0.14
Smoking cessation since the recruiting event (vs. no)	1.03 (0.85–1.24), *P* = 0.76
Regular physical activity (vs. no)	0.88 (0.79–0.99), *P* = 0.033
Reduction of fat intake (vs. no)	0.97 (0.85–1.10), *P* = 0.60
Increased consumption of fruit and vegetables (vs. no)	0.86 (0.76–0.98), *P* = 0.019
Reduction of alcohol intake (vs. no)	0.95 (0.85–1.06), *P* = 0.37
Attended a cardiac rehabilitation programme (vs. no)	0.83 (0.73–0.94), *P* = 0.0026
Overweight (vs. normal weight)	0.95 (0.81–1.11), *P* = 0.54
Obesity (vs. normal weight)	1.03 (0.88–1.20), *P* = 0.71
Abdominal overweight (vs. normal waist)	1.07 (0.89–1.28), *P* = 0.48
Central obesity (vs. normal waist)	1.17 (1.00–1.36), *P* = 0.049
Previous hospitalization for CABG (vs. no)	1.10 (0.96–1.25), *P* = 0.18
Previous hospitalization for PCI (vs. no)	1.16 (1.03–1.31), *P* = 0.018
Previous hospitalization for stroke (vs. no)	1.61 (1.33–1.95), *P* < 0.0001
Previous hospitalization for heart failure (vs. no)	1.52 (1.29–1.79), *P* < 0.0001
Previous diagnosis of PAD (vs. no)	1.70 (1.38–2.10), *P* < 0.0001
Aspirin or other anti-platelets (vs. no)	0.97 (0.77–1.21), *P* = 0.77
Blood pressure lowering drugs (vs. no)	0.95 (0.74–1.23), *P* = 0.70
Lipid-lowering drugs (vs. no)	0.89 (0.77–1.03), *P* = 0.13
Drug adherent (vs. no)	0.97 (0.81–1.16), *P* = 0.77
Systolic blood pressure (per 10 mmHg)	1.01 (0.98–1.04), *P* = 0.49
Diastolic blood pressure (per 10 mmHg)	0.98 (0.93–1.03), *P* = 0.44
Resting heart rate (per 10 beats/min)	1.11 (1.06–1.17), *P* < 0.0001
Log(eGFR) (per 1 unit on log(eGFR scale))	0.68 (0.58–0.79), *P* < 0.0001
Total cholesterol (per mmol/L)	1.04 (0.99–1.09), *P* = 0.082
LDL cholesterol (per mmol/L)	1.03 (0.98–1.09), *P* = 0.26
Non-HDL cholesterol (per mmol/L)	1.07 (1.03–1.11), *P* = 0.0010
Controlled diabetes (vs. no diabetes)	1.14 (0.97–1.34), *P* = 0.11
Uncontrolled diabetes (vs. no diabetes)	1.65 (1.43–1.89), *P* < 0.0001
HADS anxiety score 8–10 (vs. < 8)	1.18 (1.01–1.37), *P* = 0.0312
HADS anxiety score ≥ 11 (vs. < 8)	1.41 (1.20–1.66), *P* < 0.0001
HADS depression score 8–10 (vs. < 8)	1.36 (1.18–1.57), *P* < 0.0001
HADS depression score ≥ 11 (vs. < 8)	1.48 (1.23–1.78), *P* < 0.0001
Moderate risk country of recruitment (vs. low risk)	1.34 (1.16–1.56), *P* < 0.0001
High risk country of recruitment (vs. low risk)	1.77 (1.51–2.08), *P* < 0.0001
Very high risk country of recruitment (vs. low risk)	2.34 (1.96–2.78), *P* < 0.0001

[a]Adjusted for age and country risk.

counselling should be a crucial component of modern cardiac prevention and rehabilitation programmes.[23,24]

In our population of CHD patients, most of whom were taking antihypertensive drugs, baseline levels of blood pressure were not associated with adverse outcomes, an observation in line with data from the REACH registry.[25] Raised non-HDL cholesterol emerged as a much stronger independent prognostic risk factor than LDL cholesterol in our analyses. This observation is fully in line with results from numerous studies documenting that non-HDL is superior to LDL cholesterol in predicting fatal and non-fatal events in patients with CHD or in patients treated with statins in general.[26–29] Suboptimal renal function emerged as strong independent risk factor for future development of fatal and non-fatal cardiovascular events. Both in the CLARIFY registry and the SMART study, low eGFR was retained in the final model as a highly significant predictor of adverse cardiovascular outcomes.[8,30] Apart from renal insufficiency, other comorbidities play an important role in the development of new events. Incidences of cardiovascular events were significantly and independently higher in patients with

Table 4 Results of the multivariate Weibull models in the derivation sample and in the complete sample

	Derivation sample[a]		Complete sample[b]	
	β (standard error)	Significance	β (standard error)	Significance
Constant	-3.22934 (0.63779)	$P < 0.0001$	-2.99917 (0.50091)	$P < 0.0001$
Age	+0.01849 (0.00675)	$P = 0.0062$	+0.01612 (0.00533)	$P = 0.0025$
Previous hospitalization for stroke	+0.33333 (0.10234)	$P = 0.0011$	+0.32773 (0.08145)	$P < 0.0001$
Previous hospitalization for heart failure	+0.30759 (0.08650)	$P = 0.0004$	+0.31920 (0.06765)	$P < 0.0001$
Previous diagnosis of PAD	+0.41259 (0.10968)	$P = 0.0002$	+0.38492 (0.08506)	$P < 0.0001$
Previous hospitalization for PCI	+0.19723 (0.06655)	$P = 0.0030$	+0.17003 (0.05234)	$P = 0.0012$
Controlled diabetes	+0.07061 (0.08522)	$P = 0.41$	+0.11159 (0.06597)	$P = 0.091$
Uncontrolled diabetes	+0.40276 (0.07459)	$P < 0.0001$	+0.35613 (0.05967)	$P < 0.0001$
Non-HDL-C (per mmol/L)	+0.06408 (0.02383)	$P = 0.0072$	+0.04805 (0.01981)	$P = 0.015$
Log(eGFR) (per 1 unit)	-0.29576 (0.08746)	$P = 0.0007$	-0.29937 (0.06868)	$P < 0.0001$
HADS depression score	+0.02225 (0.00995)	$P = 0.025$	+0.02385 (0.00783)	$P = 0.0023$
HADS anxiety score	+0.16749 (0.05443)	$P = 0.0021$	+0.13594 (0.04307)	$P = 0.0016$
HADS anxiety score × age	-0.00231 (0.00086)	$P = 0.0073$	-0.00179 (0.00068)	$P = 0.0088$
Moderate-risk country of recruitment	+0.24669 (0.07893)	$P = 0.0018$	+0.26532 (0.06301)	$P < 0.0001$
High-risk country of recruitment	+0.49532 (0.08697)	$P < 0.0001$	+0.51693 (0.06917)	$P < 0.0001$
Very high-risk country of recruitment	+0.76400 (0.09478)	$P < 0.0001$	+0.77499 (0.07560)	$P < 0.0001$

PAD, peripheral artery disease.
[a]Scale parameter = 0.8316.
[b]Scale parameter = 0.8252.

heart failure, stroke and those with a diagnosis of PAD, diabetes or a previous hospitalization for PCI. Dysglycaemia is prevalent in a majority of coronary patients either as diabetes, impaired fasting glycaemia or impaired glucose tolerance, many of these going undetected.[31] The poorer prognosis of CHD patients with dysglycaemia emphasizes the importance of screening and optimal glycaemic control as well as effective treatment of concomitant risk factors.

The parsimonious model that we obtained in the derivation sample including all significant risk factors, indicated excellent discrimination and calibration certainly given the age-restriction of 75 years which we used since higher age typically relates to a better discriminative value of a predictive model. This model applied to the internal validation cohort fitted equally well showing a similar discriminative ability and a very good calibration, hence demonstrating its robustness. Despite the fact that no data on anxiety and depression were available in the SWEDEHEART register and scores for each HADS scale had to be imputed by a single value hence reducing between-patients variability in predicted risk, discriminative power of our risk model was found to be good in the external validation.

The SMART Risk Score tool is currently recommended on the European Society of Cardiology (ESC) website (https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/SMART-Risk-Score) to assess residual risk in CVD patients.[8] However, refitted in the complete sample of patients, our final cross-validated EUROASPIRE risk model seems to outperform the SMART model (specifically for SMART-CAD patients) in the prediction of a composite endpoint of CVD death, non-fatal MI, or stroke, across deciles of predicted SMART risk (Supplementary material online, *Figure SA*). EUROASPIRE estimates are well in line with observed rates while SMART underestimates risk in nearly all SMART risk deciles. However, this comparison may to some extent be prone to 'optimism', the false impression of a model's performance by applying it to the same sample as it was derived from.[32] SMART's main limitation of being developed on local Dutch data only, is further illustrated with only minimal variation in risk estimates across countries (Supplementary material online, *Figure SB*).

The main strength of the EUROASPIRE surveys is the methodological approach with interviews and examinations done by centrally trained personnel using standardized procedures and equipment and with a central laboratory doing all biochemical analyses. Also, our observations are based on patients recruited from a large number of hospitals and cardiac centres from different geographical areas across Europe. However, participating centres within a country may not be fully representative for the existing healthcare infrastructure in that country. Also, we should consider the impact of a rather low participation rate of 56%, mainly explained by restrictions imposed by local ethics committees and privacy laws, which may have introduced selection bias. Finally, the relatively short period of follow-up allowed us to calculate 2 years risks only but these estimations are reliable and robust for this time interval. A risk horizon of 2 years is shorter than the more familiar 5 or 10 years associated with primary prevention scores, but risks are higher in secondary prevention and patients generally older.

There are several aspects highlighting the potential value of an accurate risk prediction model in secondary cardiovascular prevention. Despite the fact that all CHD patients should be regarded as at high risk, there are several situations in clinical practice where further risk stratification is warranted to apply more individually tailored therapeutic interventions in those at very high residual risk. The availability of a

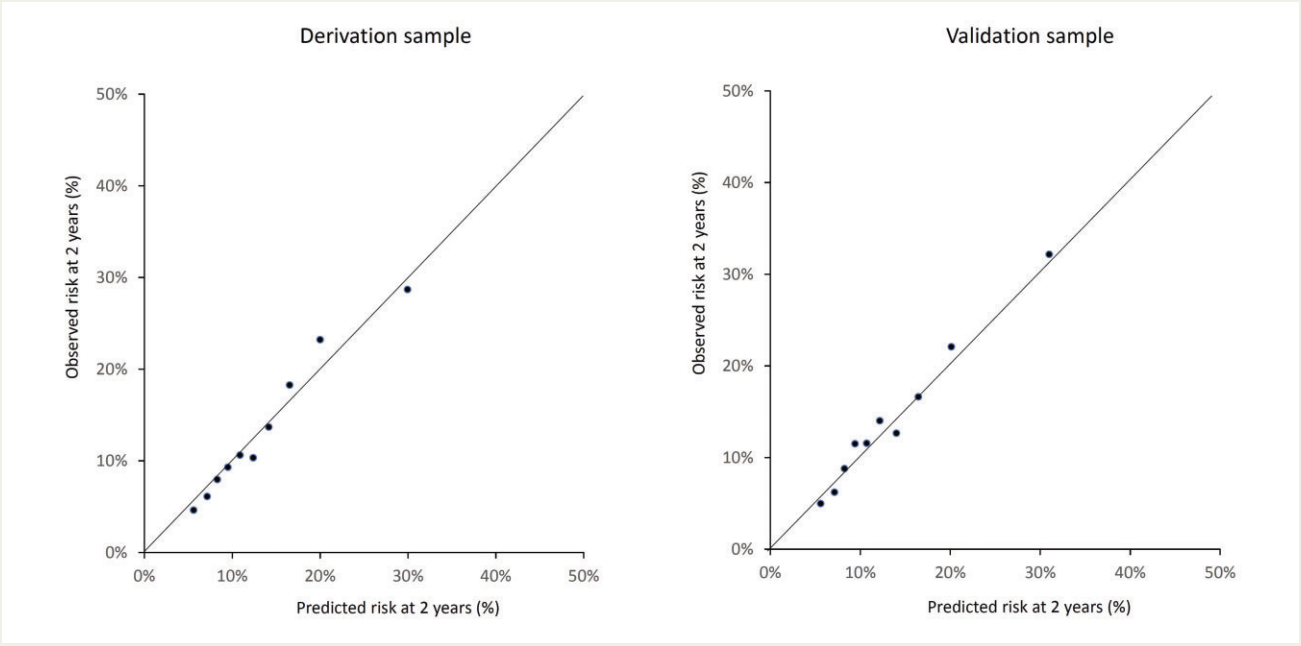

Figure 2 (*A*) Agreement between observed and predicted risk in the derivation sample across deciles of predicted risk. (*B*) Agreement between observed and predicted risk in the validation sample across deciles of predicted risk.

validated risk tool identifying those at very high multifactorial risk, is a valuable step forward in that direction, certainly in settings were resources are low. For instance, those at the lowest risk could be offered a home-based secondary prevention and rehabilitation programme while those at the highest risk may qualify for more specialized hospital-based prevention and rehabilitation services. A risk score informing patients of their residual risk may also encourage them to better adhere to their therapeutic regimen and to intensify modifications of adverse lifestyles which may have partially been the cause of their underlying disease. Finally, such a score could be used by trialists in selecting patients at very high risk to evaluate new treatments or procedures.

In conclusion, the results of this prospective follow-up of stabilized CHD patients participating in the EUROASPIRE IV and V studies indicate that the risk of recurrent cardiovascular events is mainly driven by comorbidities including diabetes, renal insufficiency, and dyslipidaemia. Controlling levels of depression and anxiety seems essential to further avoid recurrent events. Based on these findings we developed an evidence-based 'EUROASPIRE Risk Calculator' which may help health professionals to better identify CHD patients at very high risk who should be prioritized, as they require more intensive lifestyle interventions, rigorous risk factor control, and optimization of cardioprotective therapies to protect them from further fatal and non-fatal cardiovascular events. From this perspective, the risk tool we present may serve as a further step towards bridging the well-documented gap in secondary prevention.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Data availability

The database containing individual data of all patients participating in the EUROASPIRE IV and V surveys is property of the European Society of Cardiology (ESC), EURObservational Research Programme (EORP), and cannot be shared publicly.

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