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Estimation of 10-Year Risk of Death from Coronary Heart Disease, Stroke, and Cardiovascular Disease in a Pooled Analysis of Japanese Cohorts: EPOCH-JAPAN

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Aims: We aimed to develop and validate risk prediction models to estimate the absolute 10-year risk of death from coronary heart disease (CHD), stroke, and cardiovascular disease (CVD).

Methods: We evaluated a total of 44,869 individuals aged 40–79 years from eight Japanese prospective cohorts to derive coefficients of risk equations using cohort-stratified Cox proportional hazard regression models. Discrimination (C-index) of the equation was examined in each cohort and summarised using random-effect meta-analyses. Calibration of the equation was assessed using Hosmer-Lemeshow chi-squared statistic.

Results: Within a median follow-up of 12.7 years, we observed 765 deaths due to CVD (276 CHDs and 489 strokes). After backward selection, age, sex, current smoking, systolic blood pressure (SBP), proteinuria, prevalent diabetes mellitus, the ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDLC), interaction terms of age by SBP, and age by current smoking were retained as predictors for CHD. Sex was excluded in the stroke equation. We did not consider TC/HDLC as a risk factor for the stroke and CVD equations. The pooled C-indices for CHD, stroke, and CVD were 0.83, 0.80, and 0.81, respectively, and the corresponding *p*-values of the Hosmer-Lemeshow tests were 0.18, 0.003, and 0.25, respectively.

Conclusions: Risk equations in the present study can adequately estimate the absolute 10-year risk of death from CHD, stroke, and CVD. Future work will evaluate the system as an education and risk communication tool for primary prevention of CHD and stroke.

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Key words: Coronary heart disease, Stroke, Cardiovascular disease, Mortality, Prediction model

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death, accounting for 31.8% of total global deaths in 2017, which has increased by 21.1% over the past decade along with population aging[1, 2]. There is a pressing need for early CVD prevention to reduce increasing disease burden. A risk prediction model based on routinely collected medical data is a common tool for identifying high-risk individuals and planning interventions[3-5]. However, existing risk equations, which were derived mainly from white or

black descendants in the USA or European countries, reportedly perform poorly in other populations of different risk levels[6-8]. For example, Japan experienced a rapid decline in haemorrhagic stroke occurrence[9] until around 1990 and has since attained the lowest incidence and mortality rate of CVD among the Organisation for Economic Cooperation and Development countries. In addition, the case mix of CVD in Japan is also substantially different from that of Western populations[10, 11], with stroke and lacunar stroke being more prevalent than coronary heart disease (CHD)[12, 13] and large-artery occlusion[14, 15], respectively. Therefore, it would be relevant to construct ethnicity-specific prediction models of CVD outcomes based on more recent epidemiological data.

Although mortality is influenced by advances in medical technology and accessibility and quality of health care under any given incidence, CVD death rates are reportedly well proportioned to occurrences in specific populations[16]. Risk equations using death as the outcome can be easily recalibrated and updated for different populations because death statistics are usually more readily available and reliable than disease incidence. In addition, differences in surveillance methods may introduce systematic bias when associating risk factors with these endpoints, as well as absolute risks. However, it is often difficult to employ or find studies using common incidence surveillance methods between different countries and even within a country.

To date, there are only three risk equations available in the primary medical setting to predict absolute risk of CVD death: the NIPPON DATA 80 risk chart, SCORE[11], and Globorisk[17]. The latter two were derived from individual meta-analysis of multiple cohorts in Western countries with a wide span in baseline year (1972–1991 and 1948–1993, respectively), and are the most widely used risk charts. The NIPPON DATA 80 risk chart for Japan was also developed early with a baseline year of 1980[18].

Aim

In this pooled analysis of individual-level data for 44,869 Japanese, encompassing residential (rural and urban) and occupational cohorts with baseline year 1988–2002, we aimed to develop and validate risk prediction equations to estimate the absolute 10-year risk of death from CHD, stroke, and CVD combined. In addition to conventional predictors employed in earlier studies, we considered proteinuria[19] and interaction terms for all variables by sex and age[20].

Methods

Study Population

Of the 15 cohorts participating in the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan research group (EPOCH-JAPAN), we excluded one cohort with a baseline year earlier than 1985, one cohort with a median follow-up of less than 10 years, and five cohorts without baseline information on high-density lipoprotein cholesterol (HDLC), proteinuria, and prevalent diabetes mellitus (DM). The remaining cohorts consisted of two urban community-based cohorts (Suita, Osaka), three rural community-based cohorts (Hisayama, JMS, Osaki), one nation-wide general population sample cohort (NIPPON DATA 90), and two occupational cohorts (YKK, Aichi), with a total of 34,552 women and 31,214 men. We further excluded those aged <40 years or ≥ 80 years ($N=10,579$), those with missing data for any risk factor ($N=8,392$), and those with reported history of CVD at baseline ($N=1,926$), leaving 23,378 women and 21,491 men for the final analysis.

All participants provided informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethical Review Committee of Keio University (20110192), and Shiga University of Medical Science (23-125-1).

Follow-Up

Subjects in each cohort were followed up prospectively from baseline. For some cohorts, causes of death were determined by reviewing the death certificate or referring to the National Vital Statistics with further review of medical records or autopsy reports. The underlying cause of death was coded according to the International Classification of Disease (ICD) for National Vital Statistics based on the criteria proposed by the World Health Organization. These classifications were based on the ICD-9 until the end of 1994 and on the ICD-10 from the beginning of 1995. In the present study, death from CHD was defined as ICD-9:410-414, ICD-10: I20-I25; death from stroke was defined as ICD-9: 430-438, ICD-10: I60-I69; and death from CVD was defined as a combination of

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Table 1. Baseline characteristics of the participating cohorts (means (standard deviation) or percentage), EPOCH-JAPAN Study

Cohort	*N*	Baseline year	Age (years)	Men (%)	Current smoking	SBP (mmHg)	TC (mg/dl)	HDLC (mg/dl)	TC/ HDLC	Proteinuria +	Prevalent DM +
Hisayama	2,475	1988	57.5 (10.4)	42.5	25.2	132.4 (20.4)	207.0 (42.0)	50.4 (11.7)	4.3 (1.2)	5.7	8.8
NIPPON DATA 90	5,367	1990	56.1 (10.5)	42.8	28.1	138.3 (20.3)	206.6 (37.9)	53.8 (15.4)	4.1 (1.4)	2.8	4.3
YKK	2,797	1990	47.1 (5.3)	67.4	39.2	119.2 (15.7)	202.6 (35.0)	52.9 (13.2)	4.1 (1.2)	4.0	2.5
Suita	5,016	1991	58.6 (10.7)	47.5	29.3	129.8 (22.0)	210.8 (37.1)	52.7 (13.8)	4.3 (1.3)	6.1	4.6
JMS	9,535	1994	57.3 (9.1)	38.7	21.9	130.3 (20.7)	194.2 (34.7)	51.2 (12.9)	4.0 (1.2)	1.8	3.0
Osaki	10,898	1995	61.5 (9.4)	47.6	26.0	131.2 (17.5)	204.0 (35.2)	51.7 (12.8)	4.2 (1.2)	1.7	5.5
Osaka	4,767	1996	57.3 (9.6)	36.3	23.7	135.4 (20.5)	213.4 (36.7)	59.4 (14.8)	4.3 (9.3)	2.0	3.5
Aichi	4,014	2002	50.1 (5.6)	81.2	31.1	127.4 (15.7)	211.7 (34.8)	58.7 (15.8)	3.8 (1.1)	2.3	6.7
Overall	44,869	—	57.0 (10.1)	47.9	26.7	131.1 (19.8)	204.8 (36.7)	53.4 (14.1)	4.1 (3.2)	2.8	4.6

SBP indicates systolic blood pressure; TC, total cholesterol, HDLC, high-density lipoprotein cholesterol; DM, diabetes mellitus

CHD and stroke.

Statistical Analysis

Age, sex, systolic blood pressure (SBP), current smoking, proteinuria, and prevalent DM were considered as potential predictors for all end-points, whereas blood lipid indices including total cholesterol (TC), HDLC, non-HDLC, and ratio of TC to HDLC (TC/HDLC) were considered only for CHD, i.e., not for stroke or CVD, due to the inverse relationship observed for intracerebral haemorrhagic and ischemic strokes[4]. Non-normally distributed continuous variables, namely age, SBP, and blood lipid indices, were logarithmically transformed to obtain a better fit. Prevalent diabetes mellitus was defined by the World Health Organization diagnostic criteria as any one of the following essential conditions: fasting blood glucose ≥ 126 mg/dl, non-fasting blood glucose ≥ 200 mg/dl, HbA1c ≥ 6.5%, or using medication for diabetes. Female sex, non-current smoking status, negative or trace proteinuria, and non-prevalent DM per cohort was set as the reference group. Data were analysed collectively in men and women, but the model also included sex. All interaction terms of all variables listed above by sex and age were considered as potential predictors in the risk prediction model.

Cox proportional hazards regression models stratified by cohort were used to estimate variables coefficients, assuming variable effects were constant across cohorts. Since study area and cohort are highly correlated in the present study, we did not treat area as an additional stratification variable or an adjusted confounder. The statistical procedure used to determine the final predictors for each end point was similar to that used in the Framingham Study multivariable statistical models to estimate CHD risk[21]. All significant ($p<0.10$) risk factors and interaction terms identified in a series of univariable models were entered into a multivariate model with backward selection procedure (retention criteria: $p<0.10$). The mean baseline survival rate $S_0(t)$ at the 10-year follow-up from each cohort was derived and then averaged by weighting the corresponding number of deaths from each cohort to obtain the pooled baseline survival function.

The discrimination of the equation was estimated using Harrell's overall C-index for survival analysis[22] and standard error was calculated following the method introduced by Pencina *et al.*[23]. A C-index using 100-sample bootstrap sampling was calculated within each individual cohort, which was then pooled using a random-effect meta-analysis to obtain the pooled C-index. The model was calibrated by ranking subjects into deciles of predicted risk, then comparing observed and predicted event percentages within the 10-year follow-up according to a modified Hosmer-Lemeshow chi-squared statistic introduced by D'Agostino and Nam[24] with eight degrees of freedom.

Since absolute risk is often difficult to interpret, we present sex- and five-year age group-specific reference values defined as the average of the estimated risks of all individuals in that category in the present study.

All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

The baseline mean (standard deviation) values for age, SBP, TC, HDLC, and TC/HDLC were 57.0 (10.1) years, 131.1 (19.8) mmHg, 204.8 (36.7) mg/dl, 53.4 (14.1) mg/dl, and 4.1 (3.2), respectively. The proportion (%) of men, current smokers, those with proteinuria, and those with prevalent DM were 47.9, 26.7, 2.8, and 4.6, respectively **(Table 1)**.

Table 2. Coefficients and standard errors of variables included in the final model from multivariable Cox hazard regression analysis, EPOCH-JAPAN Study

	Coronary heart disease		Stroke		Cardiovascular disease	
	β (standard error)	*p* value	β (standard error)	*p* value	β (standard error)	*p* value
Ln-age (years)	61.19918 (15.75274)	0.0001	37.40606 (12.30594)	0.002	45.54988 (9.75022)	<0.0001
Men vs. women	0.65869 (0.14501)	<0.0001	—	—	0.30093 (0.08433)	0.0004
Current- vs. non-smoking	15.36389 (4.34143)	0.0004	8.24292 (3.27491)	0.01	10.64932 (2.59050)	<0.0001
Prevalent DM (+) vs. (-)	0.56252 (0.19977)	0.005	0.45679 (0.15697)	0.004	0.49413 (0.12339)	<0.0001
Proteinuria vs. (trace/-)	0.58243 (0.22974)	0.01	0.63621 (0.18467)	0.0006	0.62120 (0.14385)	<0.0001
Ln-SBP (mmHg)	46.36999 (13.31927)	0.0005	26.39953 (10.44811)	0.01	33.30729 (8.26619)	<0.0001
Ln-TC/HDLC	0.35931 (0.18845)	0.057	—	—	—	—
Ln-age × Ln-SBP	–10.61448 (3.17158)	0.0008	–5.92290 (2.48755)	0.02	–7.54461 (1.96807)	0.0001
Ln-age × Current smoking	–3.51974 (1.03357)	0.0007	–1.84505 (0.78233)	0.02	–2.41998 (0.61808)	<0.0001
S_0 (t)	0.9981		0.9961		0.9942	

Ln indicates natural logarithm; DM, diabetes mellitus; SBP, systolic blood pressure; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol

Table 3. Sex-specific mean 10-year risk (%) of death from coronary heart disease, stroke, and cardiovascular disease according to 5-year age groups, EPOCH-JAPAN Study

Age range (years)	Coronary heart disease		Stroke		Cardiovascular disease	
	Women	Men	Women	Men	Women	Men
40–44	0.008	0.06	0.02	0.06	0.03	0.11
45–49	0.02	0.12	0.07	0.13	0.08	0.24
50–54	0.06	0.26	0.17	0.28	0.21	0.51
55–59	0.13	0.50	0.36	0.58	0.45	1.03
60–64	0.28	0.89	0.74	1.09	0.94	1.89
65–69	0.55	1.38	1.39	1.78	1.76	3.03
70–74	1.04	2.29	2.55	3.01	3.25	5.05
75–80	1.84	3.63	4.38	4.83	5.60	8.00

During a median follow-up of 12.7 years, 765 (325 women, 440 men) died from CVD (276 from CHD (91 women, 185 men) and 489 from stroke (234 women, 255 men). **Supplementary Table 1** shows the crude hazard ratios of each risk factor for each end point. Neither TC nor non-HDLC were significant predictors of CHD death in the crude model ($p>0.10$). After backward variable selection, the final model for CHD included age, sex, SBP, current smoking, proteinuria, prevalent DM, TC/HDLC, and interactions of age by SBP and age by current smoking. HDLC did not remain a significant predictor of CHD death in the multivariable model with or without TC/HDLC. The final model for stroke included age, SBP, current smoking, proteinuria, prevalent DM, and interactions of age by SBP and age by current smoking. Further, the same predictors, as well as sex, were retained in the final model for CVD. All interaction terms of sex by variables were removed from the final models. The coefficients and standard errors of all predictors for each end point are presented in **Table 2**.

Women aged 70–74 years on average had a 1.04%, 2.55%, and 3.25% risk of death from CHD, stroke, and CVD within 10 years, respectively **(Table 3)**. Men aged 65–69 years had a 1.38%, 1.78%, and 3.03% risk of death from CHD, stroke, and CVD, respectively.

The pooled C-index at 10-year follow-up for CHD, stroke, and CVD were 0.83 (0.66–1.05), 0.80 (0.67–0.95) and 0.81 (0.70–0.93), respectively. There was no heterogeneity in discrimination across individual cohorts in all three end points. The *p*-values of Hosmer-Lemeshow tests indicating model calibration for CHD, stroke, and CVD were 0.18, 0.003, and 0.25, respectively **(Fig. 1a–c)**. When model performance was measured according to sex, the corresponding C-indices were 0.86 (0.56–1.32), 0.79 (0.61–1.02), and 0.81 (0.65–1.00) for women, and 0.78 (0.58–1.06), 0.79 (0.61–1.03), and 0.79 (0.65–0.95)

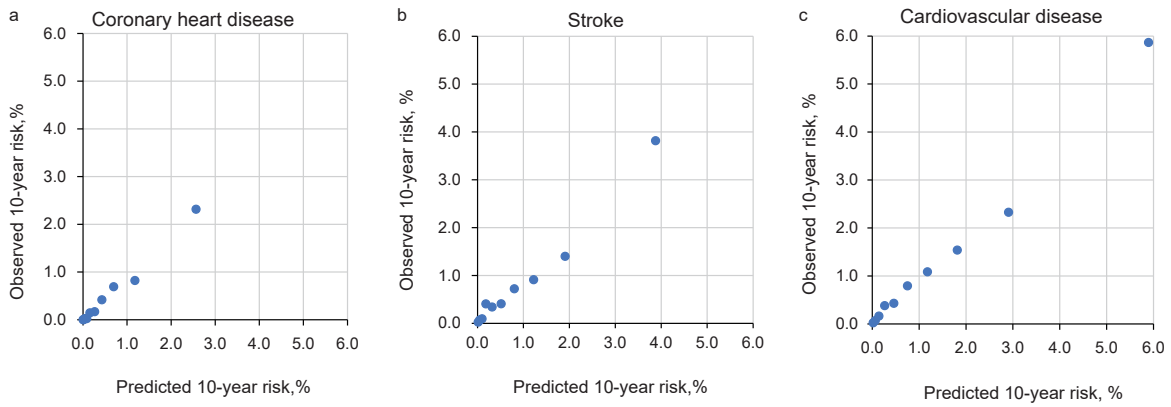

Fig. 1.

Calibration plots for death from coronary heart disease (a), stroke (b), and cardiovascular disease (c), showing predicted and observed 10-year risk according to deciles of predicted 10-year risk. Solid points denote each decile.
(a). Coefficient of the regression = 0.8725, constant of the regression = –0.0238, R^2 = 0.9866. Calibration for x^2 = 11.39, p = 0.18.
(b). Coefficient of the regression = 0.9289, constant of the regression = –0.0172, R^2 = 0.9745. Calibration for x^2 = 23.69, p = 0.003.
(c). Coefficient of the regression = 0.9573, constant of the regression = –0.0249, R^2 = 0.9889. Calibration for x^2 = 10.20, p = 0.25.

for men, respectively. The corresponding p-values of the Hosmer-Lemeshow test were 0.27, 0.002, and 0.04 for women, and 0.51, 0.49, and 0.25 for men, respectively (data not shown).

Discussion

We developed risk equations to estimate the absolute 10-year risk of death from CHD, stroke, and CVD using relatively contemporary healthy Japanese population cohorts. The models performed well in men and women for discrimination across all end points. Deciles of predicted 10-year risk generally matched well with observed risk for all end points in men, but are likely suboptimal for stroke and CVD in women.

Prediction models for CHD, stroke, and CVD incidence have been reported in Japan[25-29]. The primary advantage when using mortality as the endpoint is that mortality statistics are readily available domestically in Japan as well as internationally. Further, they can be standardized across different populations, which facilitates model recalibration to different times and populations[30]. We recognize that it would be straightforward to develop an incidence model that aids primary prevention effort. However, mortality models can be more easily updated or recalibrated for specific places at different times.

Regardless of the types of endpoints, these risk-estimation systems, including ours, can aid decision-making for clinicians to deliver appropriate care for patients according to their absolute risks and also allow them to better communicate disease risks with patients to help modify behaviour, including receiving pharmacological interventions. However, the benefits of implementing such systems to better control risk factors have not yet been entirely elucidated. One approach is to present risk as years of life lost for the individual's actual age[31, 32]. As a previous study from Japan proposed the use of vascular age[33], we have presented average risks of all individuals in five-year age groups in each sex as reference risk values to better communicate a patient's risks.

The present study included common risk factors for CVD and observed positive associations of age, SBP, current smoking, and prevalent DM with CHD and stroke death. The finding is consistent with those of previous studies using incidence or mortality of CHD, stroke, or CVD as end-points[34]. The stronger associations for SBP, current smoking, and prevalent DM with CHD death than stroke death were consistent with findings from another larger scale contemporary Japanese study[35]. Further prospective studies supported interaction effect of age by SBP on CHD or stroke[20, 36], as well as age by current smoking on CHD[37] or stroke[38].

While proteinuria has been increasingly recognised as an important risk factor for CHD[19, 39], stroke[19], and CVD[40] across diverse populations, it has never been incorporated into existing risk prediction models for long-term CVD. Because proteinuria can be easily and inexpensively detected using a urine dipstick test, our predictive model that included proteinuria can be applied to primary care settings.

TC is the most widely used variable related to lipid metabolism in prediction models for incident CVD[34] or CVD death, including SCORE, Globorisk, and NIPPON DATA 80[11, 17, 18]. Indeed, the US latest

lipid guidelines[41] recommended lipid screening for primary prevention of CVD with TC and HDLC. We examined several combinations of lipid markers in the present study and found that only TC/HDLC but not TC, HDLC, or non-HDLC, was a significant predictor of CHD death. This finding is consistent with the SCORE model that included TC/HDLC. Although the latest Japanese guidelines recommend using LDLC for screening[4], we did not examine LDLC as it could not be calculated using the Friedewald equation[42] in cohorts without fasting blood sampling. The reasons for not observing positive associations of TC or non-HDLC alone with CHD are unclear; however, we found that low TC was a poor prognostic factor in CHD patients[43, 44], most likely because we used CHD death as the outcome. Another possibility may be the broader use of statins for primary and secondary CHD prevention, as the present study consisted of more recent cohorts compared to previous SCORE[11] and NIPPON DATA 80 cohorts[18]. However, limited data on cholesterol-lowering therapy during follow-up in the present study inhibited further interpretation.

Our stroke model included similar predictors to those in previous Japanese studies of stroke incidence[33] and showed good discrimination performance. However, our stroke prediction model may lack accuracy when predicting stroke death in women. Specifically, it generally overestimated risk across risk deciles. Whether further data such as antihypertensive or cholesterol-lowering medication, or female specific risk factors such as menopause, would serve to generate better goodness of fit for stroke death when building the prediction model warrants further investigation.

The C-index of the model for CVD death in the current study (0.81) was superior to those reported from SCORE's TC/HDLC risk chart[11] for low-risk region (0.75), SCORE's TC risk chart (0.74), and Globorisk[17] for fatal CVD (0.76). Yet we could not compare our results with those in the NIPPON DATA 80 [18] as it did not report internal validation results. The C-indices of CHD and the stroke model in the present study were 0.85 and 0.80, which were comparable to prediction models in a recent large-scale Japanese cohort: incident CHD[29], 0.81 and incident stroke[33], 0.78.

The present study is subject to some limitations. First, developing the risk equation relied solely on baseline measurements of risk factors, which may have attenuated effect size estimates. Second, our model did not include medication for dyslipidemia due to unavailable variables in many of our cohorts, which may have led to less accurate predictions.

Our study integrated individual participant data from multiple high-quality prospective cohorts using a relatively recent baseline year. The large sample size enabled us to build separate prediction models for CHD and stroke. Including a diverse population encompassing residential (urban and rural) and occupational cohorts ensured a representative sample of the general population, which increased model applicability to the overall Japanese population. In addition, we constructed models that included proteinuria, an approach that may expand the use of proteinuria in primary care settings and allow more accurate risk stratification.

In conclusion, the EPOCH-JAPAN risk prediction models created in the present study can adequately estimate the absolute 10-year risk of death from CHD, stroke, CVD. Therefore, they can be used as education and risk communication tools for primary prevention of CHD and stroke. Further risk factors in addition to those used in the present study may be needed for more accurate predictions for stroke in women.

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COI

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Supplementary Table 1. Univariable hazard ratios (HRs) and 95% confidence intervals (95% CIs) for death from coronary heart disease, stroke and cardiovascular disease, EPOCH-JAPAN Study

	Coronary heart disease		Stroke		Cardiovascular disease	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Ln-age (year)	1,469 (533-4,050)	<0.0001	2,486 (1,130-5,468)	<0.0001	2,047 (1,098-3,815)	<0.0001
Men vs. women	2.65 (2.06-57.06)	<0.0001	1.43 (1.19-15.25)	<0.0001	1.77 (1.53-60.09)	<0.0001
Current- vs. non-smoking	2.07 (1.63-35.26)	<0.0001	1.40 (1.16-11.93)	0.0006	1.62 (1.40-40.57)	<0.0001
Prevalent DM (+) vs. (-)	2.69 (1.82-25.09)	<0.0001	2.26 (1.67-27.42)	<0.0001	2.41 (1.90-51.64)	<0.0001
Proteinuria vs. (trace/-)	3.04 (1.95-24.38)	<0.0001	2.72 (1.90-30.11)	<0.0001	2.83 (2.15-54.25)	<0.0001
Ln-SBP (mmHg)	34.86 (16.16-75.20)	<0.0001	28.40 (15.77-51.15)	<0.0001	30.63 (19.20-48.87)	<0.0001
Ln-TC/HDLC	1.75 (1.20-2.42)	0.003	—	—	—	—

Ln indicates natural logarithm; DM, diabetes mellitus; SBP, systolic blood pressure; TC, total cholesterol; HDLC, high density lipoprotein cholesterol.

Estimated risk = 1 − $S_0(t)^{\exp(\Sigma\beta x - \Sigma\beta\bar{x})}$

$S_0(t)$ is the average survival rate at 10 years follow-up; β's are the Cox hazard regression coefficients; x's are the individual's values on the predictors and $\bar{x}$'s are the mean values of the predictors of population.

$S_0(t)$ for coronary heart disease = 0.9981; $S_0(t)$ for stroke = 0.9961; $S_0(t)$ for cardiovascular disease = 0.9942

Example 1: A 70-year-old, non-smoking female with prevalent DM, non-proteinuria, systolic blood pressure of 135 mmHg, total cholesterol of 185 mg/dl, high density lipoprotein cholesterol of 58 mg/dl.

$\Sigma\beta\bar{x}$ = 61.19918 × Ln(57) + 0.65869 × 0.480 + 15.36389 × 0.267 + 0.56252 × 0.046 + 0.58243 × 0.028 + 46.36999 × Ln(131.1) + 0.35931 × Ln(4.1) -10.61448 × Ln(57) × Ln(131.1) -3.51974 × Ln(57.0) × 0.267=265.45

$\Sigma\beta x$ = 61.19918 × Ln(70) + 0.65869 × 0 + 15.36389 × 0 + 0.56252 × 1 + 0.58243 × 0 + 46.36999 × Ln(135) + 0.35931 × Ln(185/58) -10.61448 × Ln(70) × Ln(135) -3.51974 × Ln(70) × 0=267.24

Estimated 10-year risk of coronary heart disease death= 1 − $S_0(t)^{\exp(\Sigma\beta x - \Sigma\beta\bar{x})}$ = 1-0.9981$^{\exp(267.24-265.45)}$ = 1.13%

Example 2: A 70-year-old, smoking male with non-prevalent DM, non-proteinuria, systolic blood pressure of 140 mmHg.

$\Sigma\beta\bar{x}$ = 37.40606 × Ln(57) + 26.39953 × Ln(131.1) + 8.24292 × 0.267 + 0.45679 × 0.046 + 0.63621 × 0.028 -5.9229 × Ln(57) × Ln(131.1) -1.84505 × Ln(57) × 0.267 = 163.44

$\Sigma\beta x$ = 37.40606 × Ln(70) + 26.39953 × Ln(140) + 8.24292 × 1 + 0.45679 × 0 + 0.63621 × 0 -5.9229 × Ln(70) × Ln(140) -1.84505 × Ln(70) × 1=165.43

Estimated 10-year risk of stroke death = 1 − $S_0(t)^{\exp(\Sigma\beta x - \Sigma\beta\bar{x})}$ = 1- 0.9961$^{\exp(165.43-163.44)}$ = 2.82%