STATE OF THE ART CORONARY HEART DISEASE RISK ESTIMATIONS BASED ON THE FRAMINGHAM HEART STUDY

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SUMMARY

The aim was to review the most interesting articles dealing with estimations of an individual's absolute coronary heart disease risk based on the Framingham heart study. Besides the Framingham coronary heart disease risk functions, results of validation studies of these Framingham risk functions are discussed. In general, the Framingham risk functions overestimated an individual's absolute risk in external (non-Framingham) populations with a lower occurrence of coronary heart disease compared with the Framingham population, and underestimated it in populations with a higher occurrence of coronary heart disease. Even if the calibration accuracy of the Framingham risk functions were not satisfying, the Framingham risk functions were able to rank individuals according to risk from low-risk to high-risk groups, with the discrimination ability of 60% and more.

Key words: Framingham heart study, coronary heart disease, risk, validation study, calibration, discrimination

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INTRODUCTION

Coronary heart disease (CHD) is the most frequent cause of death in Europe (1). In the Czech Republic, age (35–74 years) standardized mortality (computed per 100 000 European standard population) from CHD decreased from 543 in 1986 to 328 in 1998 in men and from 202 to 120 in women, respectively. Figure 1 shows the specific-country age standardized mortality from CHD in 1981 (1986 for the Czech republic) and 1998. Despite the fact that an essential decrease in CHD mortality was registered in a majority of countries, CHD still remains the main cause of death there. In the Czech Republic, the most frequent cause of death in 2003 was chronic CHD (I25 – code of diagnosis in International classification of diseases, 10th revision (ICD-10)) both in men (5 913 cases) and women (7 008 cases) (2). The development of CHD mortality in the Czech Republic shows Fig. 2.

Cigarettes smoking, elevated blood pressure, elevated serum total cholesterol, elevated serum low-density lipoprotein (LDL) cholesterol, low serum high-density lipoprotein (HDL) cholesterol, diabetes mellitus, and of course advancing age were identified as the major CHD risk factors. These risk factors are summarized with other predisposing and conditional risk factors in the publication (3). A lot of guidelines for prevention of cardiovascular diseases have been published by different organizations, e.g. by the European Society of Cardiology (4).

The first question is how to decrease cardiovascular morbidity and mortality. To start with, the aim must be to popularize health life style. Secondly individuals with cardiovascular risk factors already present should identify with the goal to intervene their risk factors. The modifiable risk factors can be controlled by changing lifestyle or by pharmacotheraphy.

The second question is how to find person at very high risk of cardiovascular diseases. Epidemiologists, statisticians and other health workers have been working on statistical models which evaluate the cardiovascular risk factors simultaneously and estimate an individual's absolute risk of developing cardiovascular diseases. The absolute risk is the probability that an individual will experience cardiovascular disease within a given time period (the ratio of absolute risks in two different groups of people is called the relative risk). These statistical models are increasingly used to identify a population at high risk.

Well-known statistical models are those derived from the Framingham Heart Study (FHS) (5–9). While FHS is based on data of the American population, e.g. the SCORE project (10) and the Danish population study (11) estimate the absolute cardiovascular risk using data from the European population.

The aim of this work was to summarize most interesting articles which have been published about estimations of CHD risk based on the data from FHS.

MATERIAL AND METHODS

Framingham Heart Study

As written in web page http://www.nhlbi.nih.gov/about/framingham/design.htm, FHS is the prospective cohort study started in 1948 and continuing up to this day. The original objective of the Framingham Heart Study was to identify the risk factors and their impact on the cardiovascular disease development. The original study cohort consisted of 5,209 respondents of a random sample of 2/3 of adults at the age of 30 to 62 years

residing in Framingham (Massachusetts, USA) in 1948. The offspring study was started in 1971 with the aim to assess cardiovascular risk factors in young adults. A sample of 5,135 men and women, consisting of the offspring of the original cohort and their spouses, was established. A third generation (the children of the offspring cohort) is currently being established with the aim to further analyse the role of genetic factors in the development of cardiovascular diseases.

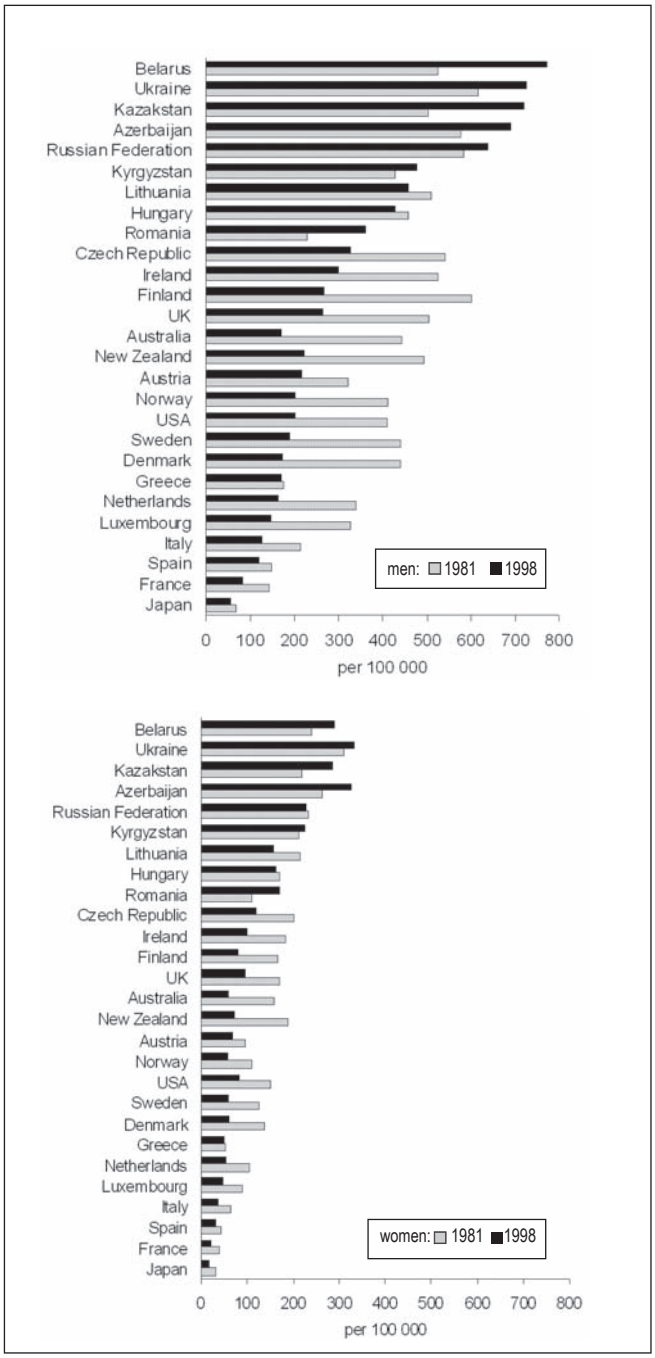

Fig. 1. *Age-standardized[1] mortality from coronary heart disease[2] (CHD), 35–74 years, 1981[3], 1998.*
[1]Using the European standard population
[2]CHD codes 410–414 (8th and 9th Revision of ICD), I20–I25 (10th Revision of ICD), ICD-International Classification of Diseases
[3]For the Czech Republic 1986 instead of 1981
Data source: World Health Organization (1)

The Framingham data were used to estimate an individual's absolute risk of developing CHD in a specific time interval. A non-proportional hazard Weibull accelerated failure time model (parametric model) and a Cox proportional hazards regression model (semiparametric model) were mainly used for individual's absolute CHD risk estimations (12). The risk of a failure within a time interval t, computed under the assumption that the individual has survived up to the beginning the time interval, is called the hazard. Both these parametric and semiparametric models allow modelling the hazard as a combination of categorical and quantitative variables, so-called explanatory variables or risk factors. The Cox proportional hazards regression assumes that the hazards are proportional. It means that the hazard of a disease at time t changes proportionately with the explanatory variables and the proportionality constant is the same for all t. In other words, the two equally-aged individuals with different levels of explanatory variables will have different hazards for developing a disease. These probabilities may increase with age, but the hazard ratio between their sets of the explanatory variable covariates is constant over time. Unlike the Cox model, the non-proportional hazard Weibull accelerated failure time model is without the assumption of proportional hazards. However, in the case of the Weibull regression, the failure time is assumed to follow the Weibull distribution. While in the Cox regression, no specific assumptions are made about the distribution.

Validation Studies

The Framingham risk functions were applied in external (i.e. non-Framingham) populations to estimate CHD risk. Tests of calibration and discrimination were used to measure the degree of an accuracy of the Framingham risk function in external populations.

Calibration of the model expresses the degree of the agreement between the observed number of CHD events and that predicted by the statistical model. It means that calibration tests verify the

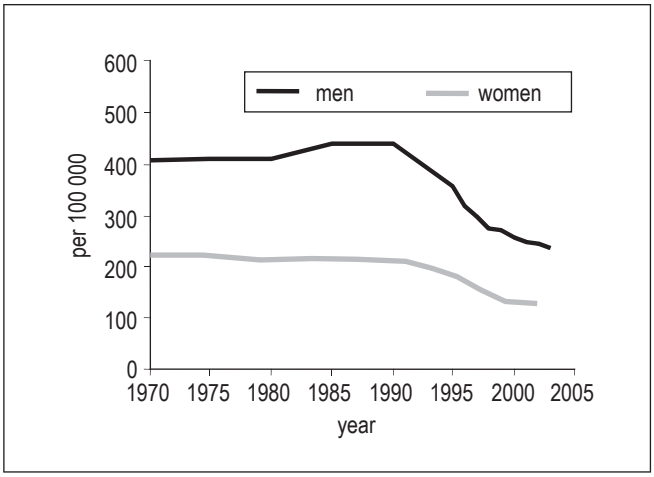

Fig. 2. *Age-standardized[1] mortality from coronary heart diseases[2] (CHD) in the Czech Republic, 1970, 1975, 1980, 1985, 1990, 1995–2003.*
[1]Using the European standard population,
[2]CHD codes 410–414 (8th and 9th Revision of ICD), I20–I25 (10th Revision of ICD), ICD International Classification of Diseases
Data source: Institute of Health Information and Statistics of the Czech Republic (2)

Table 1. *Coronary heart disease (CHD) risk estimations based on the Framingham heart study (FHS)*

Study-year of publication (citation)	FHS-1991 (5–6)	FHS-1991 (6)	FHS-1998 (7)	FHS-2000 (8)	FHS-2001 (9)
Population	**General population of Framingham (USA)**				
Baseline examination	1968–1975	1968–1975	1971–1974	1968–1987	1971–1974
Gender (sample size)	men (2,590) women (2,983)	men (2,590) women (2,983)	men (2,489) women (2,856)	men (4,823) women (5,333)	men (2,439) women (2,812)
Age (yrs)	30–74	30–74	30–74	35–74	30–74
Risk function					
Failure of interest[1]	CHD	fatal CHD	CHD	CHD	hard CHD
Time until failure (yrs)	4–12	4–12	10	1–4	5, 10[3]
Statistical method[2]	Weibull regression	Weibull regression	Cox regression	Weibull regression	Cox regression
Explanatory variables[4]					
Gender	+	+	+	+	+
Age	+	+	+	+	+
Menopause				+ (for women)	
BP			+		+
SBD/DBP	+	+		+ (SBD)	
Antihypertensive therapy				+	
Cigarette smoking	+	+	+	+	+
Total cholesterol	+	+	(+)	+	+
HDL-cholesterol	+	+	+	+	+
LDL-cholesterol			(+)		
Triacylglycerols				(+) (for women)	
Diabetes mellitus	+	+	+	+	+
Left ventricular hypertrophy	+	+			
Alcohol				+ (for women)	

CHD = coronary heart disease, FHS = Framingham heart study, BD = blood pressure, SBD = systolic BP, DBP = diastolic BP, HDL = serum high-density lipoprotein, LDL = serum low-density lipoprotein

[1]CHD involves angina pectoris, coronary insufficiency, myocardial infarction, and coronary death; fatal CHD involves coronary death, hard CHD involves fatal CHD and non-fatal myocardial infarction

[2]See Table 2

[3] To estimate the 5-, 10-year risk additional information (excluding information included in the cited article) is needed from the authors of the article

[4]Variables marked with + were used for modeling the risk; in some cases the models also involve the interactions between the given explanatory variables or e.g. their quadratic term (not marked in the table, for more information and the precise definitions of the explanatory variables see the publications cited in heading); in FHS-1998 the model with total cholesterol and without LDL-cholesterol, and the model without total cholesterol and with LDL-cholesterol (+) were derived; in FHS-2000 the model with and without triacylglycerols (+) were derived for women

accuracy of an individual's risk estimate. The calibration is tested with a Hosmer-Lemeshow goodness of fit test and other goodness of fit tests (13). When the calibration fails (i.e. there is a significant difference between the observed and predicted number of CHD), a recalibration could be done. It means that the Framingham risk function could be adjusted for prevalence of risk factors and underlying rates of CHD in the external population.

Discrimination expresses the ability of the model to divide individuals at a baseline into those who will experience CHD within a specific time interval, and into those who will not. Discrimination is evaluated by a so-called receiver operating characteristic (ROC) curve plotting sensitivity of the model against specificity over all the possible values of the absolute risk estimated by the model. The area under ROC curve varies from 0 to 1. When it is 1 the model can perfectly classify individuals. The model is not better than chance if the area equals 0.5.

RESULTS

Nowadays the Framingham statistical models derived in the 90th years of the 20th century and at the beginning of the 21st century are mainly used for the CHD risk estimations. The risk functions were derived from data on gender-age specific populations and estimate the absolute risk of CHD within different long periods (Table 1). For instance, the Framingham risk functions

Table 2. *Risk estimations by regression models*

Model	Risk estimation[1]
Nonproportional hazard Weibull accelerated failure time regression model	$1-\exp\{-\exp(\frac{\ln(t)-\sum_{i=1}^{k}\beta_i x_i}{\sigma})\}$
Cox proportional hazard regression model	$1-S_0(t)^{\exp(\sum_{i=1}^{k}\beta_i x_i-\sum_{i=1}^{k}\beta_i \bar{x}_i)}$

[1]t denotes the time until the event of interest (e.g. CHD); β_i and σ represent estimated parameters, $S_0(t)$ is the average survival at time t – for their values see the publications cited in Table 1; x_i represents the explanatory variable of an individual (e.g. x_1 might be age in years)

from 1991 estimates the risk of CHD or fatal CHD, respectively, within the period from 4 to 12 years, and the function from 1998 estimates the 10-year absolute CHD risk. The Framingham risk functions assess the CHD risk in individuals without over of CVD and CHD. The explanatory variables used for modelling the risk of (fatal, hard) CHD event (the failure of interest) are also summarized in Table 1.

The statistical models used for CHD risk estimations within the specific periods are in detail introduced in Table 2.

Tables 3–5 show studies validating the Framingham risk functions in external (i.e. non-Framingham) populations. Generally, the Framingham risk function overestimated the observed number of CHD in the validation studies with a lower occurrence of CHD than in Framingham, and vice versa underestimated in the validation studies with a higher occurrence of CHD. In a very few studies the function was recalibrated, and after the recalibration the observed number of CHD was insignificantly different from that predicted.

If the ROC analysis was done, the discrimination of the Framingham risk functions in the external populations presented in Tables 3–5 was at least 0.60 (i.e. 60%). In no validation study the discrimination exceeds the threshold of 90% considered as the excellent classification accuracy.

DISCUSSION

In Table 1, the Framingham CHD risk functions were introduced. The risk calculators based on these risk functions are available in web page cited above or e.g. in web pages http://www.scopri.ch/ of Commitment to Evidence for Primary Care and in http://www.americanheart.org/ of American Heart Association. Sheridan et al. (14) examined the features of available Framingham-based risk calculation tools and review their accuracy and feasibility in clinical practice.

The validation studies of these Framingham risk function are summarized in Table 3–5. Some of the validation studies used the Framingham functions to estimate CHD risk beyond the designed period and age range (e.g. the validation study by Ramachandran et al.). Some studies verified the risk estimation in samples recruited from the profile of different population than FHS. It may be pointed out that FHS study recruited participants from residents of the town Framingham, while some validation studies were based on e.g. rural populations and employees (e.g. the validation study by Menotti et al.). A great number of validation studies was aimed at narrower age range than FHS. Generally, there were large geographic variations in coronary morbidity and mortality across the validation studies.

The Framingham CHD risk function from 1991 (5–6) (Table 3) has been also validated in the Czech Republic. The validation was conducted within the 20-year primary prevention study of atherosclerotic risk factors (STULONG) including 1,417 middle-aged men from the Czech Republic (Prague, 2nd district), and starting in 1975 (27). The STULONG study was conducted by 2nd Dep. of Internal Medicine, 1st Faculty of Medicine and General Faculty Hospital, Charles University in Prague 2 (project leader František Boudík, project coordinator Marie Tomečková). Under this study, the Framingham risk functions underestimated the real absolute risk of CHD. There are three main explanations for this result (20):

- To start with, the incidence of CHD was higher in the STULONG population than that in Framingham. Globally, mortality from CHD is lower in the USA than in the Czech Republic (Fig. 1).
- Secondly, STULONG was a primary preventive study and the risk profile of individuals in our study may therefore differ from that of the general population without primary prevention. However, we can speculate about the efficiency of the intervention: by design a true control group was lacking, nevertheless, the age-specific cardiovascular mortality in the risk group decreased over time in relation to the general population.
- Finally, the estimation of the risk may have been more precise, if the occurrence of left ventricular hypertrophy (LVH) was surveyed (LVH needed to estimate the CHD risk was assumed not to be present, Table 3). On the other hand, Anderson et al. (5) say that the estimated effect of the left ventricular hypertrophy is very large but with a large standard error because of the small prevalence of left ventricular hypertrophy in FHS.

Despite the above limitations, the Framingham risk function was able to identify high-risk men in the Czech population with the acceptable discrimination ability of 63%. On the other hand, this discrimination ability can be debatable because it is not too high.

A lot of risk tables and charts based on the Framingham CHD risk functions have been also developed, and are summarized e.g. in the publication (28). Besides CHD, there were also derived Framingham risk functions estimating an individual's absolute risk of developing e.g. myocardial infarction, stroke or cardiovascular diseases (CVD) generally (6). The CHD models for individuals with a history of CVD, who have survived the acute period after the event, have been also developed (8).

To sum up, the Framingham risk functions overestimated an individual's absolute risk in populations with lower occurrence of CHD compared with the Framingham population, and underestimated it in populations with higher occurrence of CHD. So that, if the Framingham and an external population are not homogenous with respect to prevalence of risk factors (traditional and non-traditional) of CHD, and consequently, in the occurrence of CHD events, the Framingham risk function should be recalibrated, or a new risk function derived. Even if the calibration accuracy of the Framingham risk functions was not satisfying, the Framingham

Table 3. Validation studies of the Framingham (fatal) CHD risk functions – 1991 (5, 6)

First author of validation study-year of publication (citation)	Population	Baseline examination	Gender (sample size)	Age (yrs)	Failure of interest	Time until failure (yrs)	Calibration/ Recalibration	Discrimination (ROC curve)	Comment
Menotti – 2000 (15)	Italian rural-Seven countries study of CVD	in the 1960s	men (1,656)	40–59	CHD	10	overestimation/ not done, however, new model developed	not done	the risk chart derived from the FRF-1991 validated
Ramachandran – 2000 (16)	North east English (Whickham)	1972–1974	men (751) women (949)	30–75	CHD	20	underestimation in the low–risk (≤1.5%) group/ not done	not done	the 20-year CHD risk estimated for 30–75 years aged (FRF-1991 derived for 4–12 years and 30–74 years aged); HDL-cholesterol not collected, but assumed 1.15 mmol/l for men and 1.4 mmol/l for women
Bastuji-Garin – 2002 (17)	Northern and Southern European treated hypertensives-INSIGHT study	1994–1996	men (1,971) women (2,436)	55–74	CHD	a median follow-up 3.7 years	overestimation/ not done	not done	the CHD risk within 3.7 years estimated and considered by authors as valid (FRF-1991 derived for 4–12 years)
Brindle – 2003 (18)	British urban -British regional heart study	1978–1980	men (6,643)	40–59	CHD fatal CHD	10	overestimation for both CHD and fatal CHD/good	not done	
Hense – 2003 (19)	German inhabitants and employees – MONICA Augsburg and PROCAM studies	MONICA 1984/1985 1989/1990 PROCAM 1979–1985	MONICA men (2,861) women (2,925) PROCAM men (5,527) women (3,155)	35–64	fatal CHD plus non-fatal MI	7–13	overestimation/ not done	MONICA 0.78 (men), 0.88 (women) PROCAM 0.73 (men), 0.77 (women)	
Boudík – 2005 (20)	Czech urban (Prague) – STULONG study	1979–1988	men (540)	44–62	CHD	10	underestimation/ not done	0.63	STULONG primary preventive study; LVH status not collected, but assumed not present
Wang – 2005 (21)	aboriginal Australian (Northern Territory)	1992–1995	men (356) women (331)	20–74	CHD	8–11	underestimation, most marked in women and younger adults/not done	not done	the risk for 20–74 years aged estimated (FRF-1991 derived for 30–74 years aged); LVH status not collected, but approximated

CHD = coronary hear disease (for definition see Table 1), CVD = cardiovascular diseases, FRF = Framingham risk function, HDL cholesterol = serum high-density lipoprotein, INSIGHT study = goal in hypertension treatment, LVH = left ventricular hypertrophy, MI = myocardial infarction, MONICA = Monitoring trends and determinants of cardiovascular disease, PROCAM = Prospective cardiovascular Muenster, ROC = Receiver operating characteristic, STULONG study = 20-year primary prevention study of atherosclerotic risk factors

Table 4. *Validation studies of the Framingham CHD risk function – 1998 (7)*

First author of validation study-year of publication (citation)	Population	Baseline examination	Gender (sample size)	Age (yrs)	Failure of interest	Time until failure (yrs)	Calibration/ Recalibration	Discrimination (ROC curve)	Comment
Orford – 2002 (22)	USA healthy veterans (Boston) – NAS study	not stated precisely, however NAS started in 1961and lasted 30 years	men (1,393)	30–74	CHD	10	underestimation in the low-risk (<5%) group and overestimated in the high-risk (>40%) group/ not done	0.60	
Suka – 2002 (23)	Japanese workers	1991–1993	men (5,611)	30–59	CHD	5–7	good/ not needed	0.62	the CHD risk within 5–7 years estimated (FRF–1998 derived for 10 years)
Empana – 2003 (24)	Northern Irish (Belfast) and French urban -PRIME study	1991–1993	NORTHERN IRELAND men (2,399) FRANCE men (7,359)	50–59	CHD	5	overestimation/ not done	NORTHERN IRELAND 0.66 FRANCE 0.68	the 5-year CHD risk estimated (FRF-1998 derived for 10 years)

CHD = coronary hear disease (for definition see Table 1), FRF = Framingham risk function, NAS study = Normative aging study, PRIME study = Prospective epidemiological study of myocardial infarction, STULONG study = 20-year primary prevention study of atherosclerotic risk factors, ROC = Receiver operating characteristic

Table 5. *Validation studies of the Framingham hard CHD risk function – 2001 (8)*

First author of validation study-year of publication (citation)	Population	Baseline examination	Gender (sample size)	Age (yrs)	Failure of interest	Time until failure (yrs)	Calibration/ Recalibration	Discrimination (ROC)	Comment
D'Agostiano – 2001 (9)	whites, blacks, native Americans, Japanese American men, Hispanic men – six prospective studies	not stated precisely, however, recruitments into studies in 1965–1991	men (20,985) women (11,901)	30–74	hard CHD	5	good but excluding overestimation for Japanese American men, Hispanic men and native American women/good	0.63–0.75 (men) 0.66–0.83 (women)	
Marrugat – 2003 (25)	North East Spanish (Gerona)	1995 cross-sectional study	men (709) women (771)	30–74	hard CHD	8 – population registry 1990–1997	overestimation/good	not done	applied to Gerona registry population, but prevalence of risk factors estimated on the base of cross-sectional study; the hard CHD risk within 8 years estimated (FRF – 2001 derived for 5 and 10 years)
Liu – 2003 (26)	Chinese urban and rural – Chinese multi-provincial cohort study	not stated precisely, follow-up 1992–2002	men (16,065) women (14,056)	35–64	hard CHD	10	overestimation/good	0.705 (men) 0.742 (women)	hard CHD events comprised acute MI, sudden death, and other coronary death (Hard CHD in FRF – 2001 comprised fatal CHD and non-fatal MI)

FRF – Framingham risk function, Hard CHD – hard coronary heart disease (for definition see Table 1), MI – myocardial infarction, ROC – Receiver operating characteristic

risk functions were able to rank individuals according to risk from low-risk to high-risk groups, with the discrimination ability 60% and more. In other words, the Framingham risk functions can help in searching for individuals at high risk of CHD, if they have markedly more than a fifty-fifty chance of detecting a high risk individual. The discrimination over 90% can be regarded as excellent, 80–90% as good, 70–80% as fair, 60–70% as acceptable and fewer than 60% as unsatisfying.

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