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Cardiovascular risk scores in the prediction of subclinical atherosclerosis in young adults: Evidence from the Cardiovascular Risk in Young Finns Study

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Abstract

Aims—To study the utility of risk scores in prediction of subclinical atherosclerosis in young adults.

Methods and results—Participants were 2,204 healthy Finnish adults aged 24–39 years in 2001 from population-based follow-up study Cardiovascular Risk in Young Finns. We examined the performance of the Framingham, Reynolds, SCORE (Systematic Coronary Risk Evaluation), PROCAM, and Finrisk cardiovascular risk scores to predict subclinical atherosclerosis, i.e. carotid artery intima-media thickness (IMT) and plaque, carotid artery distensibility (CDist) and brachial artery flow-mediated dilatation (FMD) 6 years later. In 6-year prediction of high IMT (highest decile or plaque), areas under the receiver operating characteristic curves (AUC) for baseline Finrisk (0.733), SCORE (0.726), PROCAM (0.712) and Reynolds (0.729) risk scores were similar as for Framingham risk score (0.728, P always ≥ 0.15). All risk scores had similar discrimination in predicting low CDist (lowest decile) (0.652, 0.642, 0.639, 0.658, 0.652 respectively, P always ≥ 0.41). In prediction of low FMD (lowest decile), Finrisk, PROCAM, Reynolds and Framingham scores had similar AUCs (0.578, 0.594, 0.582, 0.568, P always ≥ 0.08) and SCORE discriminated slightly better

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Conflict of interest

None.

(AUC=0.596, $P<0.05$). Prediction of subclinical outcomes was consistent when estimated from other statistical measures of discrimination, reclassification, and calibration.

Conclusions—CVD risk scores had equal performance in predicting subclinical atherosclerosis measured by IMT and CDist in young adults. SCORE was more accurate at predicting low FMD than Framingham risk score.

Keywords

cardiovascular risk score; subclinical atherosclerosis; ultrasound

INTRODUCTION

Atherosclerosis begins early in life. Lesions progress with age but the rate of progression and vulnerability to acute events varies between individuals(1). Single cardiovascular risk factors have modest capabilities to predict development of cardiovascular disease (CVD)(2), but risk prediction can be improved by incorporating risk factors into risk prediction models, such as the Framingham risk score(1). Risk scores are often used to stratify individuals into different groups based on their risk of developing cardiovascular events. Since CVD has long asymptomatic phase, there has been support for expansion of predictive studies of arterial disease from its clinical form to subclinical manifestation(3). Detection of subclinical atherosclerosis has been shown to be a useful method for prediction of future coronary events (4,5).

Primary prevention of CVD has clear clinical demand, since 50% of males and 64% of females who died suddenly of coronary heart disease (CHD) in the US had no previous symptoms(6). Currently, clinicians may consider estimating CVD risk in patients with Framingham or SCORE (Systematic Coronary Risk Evaluation) risk scores using data on lipids, blood pressure and smoking where elevated risk would be indication for intervention(7). Other risk prediction models have also been developed, including the Finrisk score(8), the Reynolds risk score(9, 10) and PROCAM(11). These scores have been used to estimate probability of clinically evident arterial disease primarily in mid life and among the elderly(12,13). However, given that subclinical changes have developed by young adulthood, examining the association between CVD risk scores and extent and severity of subclinical atherosclerosis at early stage is of clinical importance.

In this analysis of the Cardiovascular Risk in Young Finns study, we examine capabilities of the Framingham, SCORE, Finrisk, PROCAM and Reynolds cardiovascular risk scores in prediction of subclinical atherosclerotic outcomes in young adults measured by carotid artery intima-media thickness (IMT) and plaque, carotid artery distensibility (CDist) and brachial artery flow-mediated dilatation (FMD).

METHODS

Subjects

The Cardiovascular Risk in Young Finns Study is a multi-centre follow-up study into cardiovascular risk from childhood to adulthood. The study began in 1980 when 3,596 Finns aged 3–18 years participated in the first cross-sectional survey. In adulthood, follow-ups have been performed in 2001 and 2007. Vascular ultrasound studies were performed amongst 2,265 study subjects aged 24–39 years in 2001, and amongst 2,197 subjects aged 30–45 years in 2007. 1,803 subjects had vascular ultrasound available at both time-points and amongst them the use of lipid-lowering (N=7) and antihypertensive medication (N=43) was rare. Subjects

gave written informed consent in 2001 and 2007. The study complies with the Declaration of Helsinki and the research protocol was approved by local ethics committee.

Physical examination and self-report measures

Height and weight were measured, and body mass index (BMI) was calculated as weight(kg)/height(m)²(14). Blood pressure was measured at least three times with a random zero sphygmomanometer. Smoking status and family history of CVD were ascertained from self-report questionnaires. Subjects smoking on a daily basis were considered smokers. Parental history of myocardial infarction was reported <55 years in either parent in 2001 and <55 years in males and <65 years in females in 2007. History of stroke was reported at any age.

Blood biochemistry

Venous blood samples were drawn primarily from the right antecubital vein after an overnight fast and serum separated, aliquoted and stored at -70°C until analysis. Determination of serum triglycerides, total cholesterol and HDL-cholesterol were done as described previously(14). LDL-cholesterol was estimated by the Friedewald formula(15) in subjects with triglycerides levels <4.0mmol. Serum CRP was determined turbidimetrically (2001: CRP-UL reagent, Wako, USA, 2007: CRP Latex reagent, Olympus, Ireland) on an AU400 analyzer (Olympus, Japan).

Ultrasound measurements

Ultrasound studies were performed on the carotid and brachial arteries with Acuson Sequoia512 ultrasound mainframes (Acuson, Mountain View, California) with 13.0 MHz linear array transducer by the same single measurer in both follow-ups.

Common carotid IMT was measured on the posterior wall of the left common carotid artery approximately 10mm proximal to the carotid bifurcation. A minimum of 4 measurements were performed to calculate mean carotid IMT. The left common carotid artery and carotid bulb area were also scanned for atherosclerotic plaques, defined as distinct areas of the far and near vessel walls protruding into the lumen >50% of the adjacent intima-media layer(16).

CDist was assessed by measuring the common carotid artery diameter in end-diastole and end-systole. The proportional change between systolic and diastolic values was calculated and distensibility was expressed as the ratio between change in diameter and pulse pressure derived from concomitant brachial blood pressure(16). $CDist = [(systolic\ diameter - diastolic\ diameter) / diastolic\ diameter] / pulse\ pressure$.

Brachial FMD was examined by measuring the left brachial artery diameter both at rest and during reactive hyperemia. The increased blood flow was induced by inflating a pneumatic tourniquet placed around the forearm to a pressure of 250mmHg for 4.5 minutes and then deflating the tourniquet(16). Measurement of arterial diameter was performed at end-diastole at fixed distance from an anatomic marker at rest and 40, 60 and 80 seconds after cuff release (16). The maximum vessel diameter during dilatation was expressed as the percentage relative to resting scan.

Adverse outcome was determined as the highest decile ($\geq 90^{th}$ percentile) and/or carotid plaque for IMT (high IMT) and lowest decile ($\leq 10^{th}$ percentile) for CDist and FMD (low CDist and low FMD) in 2007.

In 2001, 57 subjects were re-examined 3 months after their original scan to assess variability in measurements. The between-visit coefficients of variation (CV) for IMT, CDist and FMD were 6.4%, 16.3% and 26.0% respectively(16).

Cardiovascular risk score classifications

We calculated the Framingham Risk Score(17), SCORE(18), Finrisk(8), Reynolds Risk score (9,10) and PROCAM(11) algorithms for each participant. Framingham and Reynolds estimate 10-year risk of any CVD event, SCORE estimates 10-year risk of fatal CVD event, Finrisk measures 10-year risk of CHD event or stroke and PROCAM estimates 10-year risk of CHD event. All risk scores include age and have different algorithms for males and females. In addition to conventional risk factors included in risk scores (smoking status, systolic blood pressure, total cholesterol, HDL-cholesterol and diabetes status), PROCAM includes parental history of myocardial infarction, LDL-cholesterol, triglycerides and data on antihypertensive medication. Finrisk includes parental history of myocardial infarction or stroke and Reynolds Risk score includes parental history of premature myocardial infarction and high-sensitivity plasma CRP(9,10). SCORE algorithm excluded diabetes status and HDL-cholesterol(18,19).

Statistical methods

Association between risk scores and ultrasound measurements—Cross-sectional (2001 and 2007) and longitudinal associations between risk scores and ultrasound measurements were examined with Spearman's correlations. These statistical analyses were performed using SAS (version 9.1.3) software and statistical significance inferred at a two-tailed P-value<0.05.

Comparison of baseline risk scores to predict 6-year subclinical atherosclerosis—We compared the utility of baseline risk scores to predict 6-year subclinical. These analyses were based on separate logistic models that included a single binary subclinical outcome with a single risk score as the predictor variable. For comparisons, we used Framingham as the reference risk score, with subsequent comparisons made between Framingham with Finrisk, SCORE, PROCAM, or Reynolds. A number of criteria, put forward by the American Heart Association(20), were used to compare performance between risk scores. The following was performed using STATA 10.1.

Model calibration

Calibration of each model within groups (tenths) was assessed using the Hosmer-Lemshow (H-L) chi-square statistic(21). Values >20 (P<0.01) suggest a lack of adequate calibration (22).

Model discrimination

Discrimination was estimated using area under the receiver operating characteristic curve (AUC) determined for each logistic regression model. Differences in AUC between Framingham and Finrisk, SCORE, PROCAM, or Reynolds risk score models was estimated using the DeLong algorithm(23).

Risk reclassification of 6-year subclinical atherosclerosis

Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to determine the extent to which Finrisk, SCORE, PROCAM or Reynolds risk scores compared with the Framingham score reassigned participants to a risk level or category that better reflected their final outcome status (case or control)(24,25). For NRI, participants were assigned to four categories reflecting their 6-year risk of the subclinical outcome. IDI is the continuous version of NRI where, instead of assigning categories of risk, differences between risk probabilities for the two models are averaged and differenced for cases and controls. A $P \leq 0.01$ for IDI comparisons suggests improved model performance(24).

RESULTS

Table 1 presents descriptive data on study subjects. Figures 1a and 1b display cumulative distributions of 10-year risk of CVD event according to Framingham, SCORE, Finrisk, PROCAM, and Reynolds risk scores in 2001 for males and females.

Association between risk scores and ultrasound measurements

Table 2 displays Spearman's correlation between 10-year risk scores and ultrasound measurements. For IMT and CDist, all correlations were significant (P always <0.001). Correlations for FMD were not consistent and either non-significant or low ($-0.07 \leq r \leq 0.09$).

Comparison of baseline risk scores to predict 6-year subclinical atherosclerosis

Table 3 displays model fit, discrimination, calibration, and reclassification indices. For the outcome of high carotid IMT or plaque, Finnrisk, SCORE, and Reynolds risk scores tended to perform equally well as Framingham, but calibration was best for the Reynolds model (lack of fit remained substantial however). PROCAM demonstrated reduced AUC, NRI, and IDI in comparison with Framingham, but only IDI was statistically significant. Finrisk performed equally with Framingham in predicting 6-year low CDist, whereas reclassification was less accurate for SCORE (IDI) and PROCAM (NRI). Although discrimination was similar between Framingham and Reynolds risk scores, NRI and IDI were more accurate when the model with Reynolds was used. For the prediction of 6-year low FMD, Finrisk and Reynolds risk scores tended to perform equally well. SCORE improved discrimination over Framingham risk score (AUC 0.596 vs. 0.568), but calibration was poorer (18.7 vs. 4.4). Reclassification was less accurate when PROCAM was used in place of Framingham to predict low FMD.

DISCUSSION

Current guidelines for primary prevention of CVD recommend initial assessment and risk stratification based on traditional risk factor scoring followed by therapeutic intervention when necessary(1). However, risk scores have been developed to predict risk of clinically evident CVD rather than subclinical changes. In our study, we found significant correlations between CVD risk scores and markers of subclinical atherosclerosis. According to AUCs, all risk scores seemed to have equal performance in prediction of high IMT and carotid plaque (P always ≥ 0.15).

Of the subclinical outcomes examined, low FMD was least well predicted by any of the risk scores. All risk scores presented lack of calibration in predicting high IMT and low Cdist, whereas prediction of low FMD did not display similar inadequacy. These findings could be partially accounted for high variability in FMD(26). However, SCORE displayed higher discrimination in prediction of low FMD than Framingham. Moreover, Finrisk, PROCAM and Reynolds risk scores had higher AUC than Framingham, although none of these differences were statistically significant. Thus, Framingham risk score might have lower performance in prediction of early endothelial dysfunction. To some extent, observation could be due to the lack of family history of CVD in Framingham compared to Finrisk, PROCAM and Reynolds. However, the significantly more discriminatory SCORE also lacked family history of CVD. Moreover, Finrisk and PROCAM displayed adverse reclassification compared to Framingham. Thus, addition of family history may not substantially improve prediction of low FMD.

All risk algorithms included age, smoking status, systolic blood pressure, total cholesterol, HDL-cholesterol and diabetes status except SCORE that excluded HDL-cholesterol and diabetes(8,17,18). Moreover, Reynolds risk score included high-sensitivity plasma CRP measurement and parental history of premature CVD(9,10). Parental history of myocardial

infarction and stroke were included in Finrisk score(8) and PROCAM included LDL-cholesterol, triglycerides, parental history of myocardial infarction and regional adjustment factor based on geographic prevalence of CVD(11). In this study, all risk scores performed equally in the prediction of 6-year high IMT and low CDis, suggesting that the additional risk factors included in Finrisk, Reynolds and PROCAM risk scores did not increase discrimination in our cohort. Moreover, although lacking HDL-cholesterol and diabetes status, SCORE displayed equal performance in predicting high IMT and better discrimination in prediction of low FMD than Framingham risk score which could be partially accounted for the European basis of SCORE.

Although Finrisk was based on a Finnish cohort and SCORE based on a European cohort, there were few differences between these and the US based Framingham risk score in prediction of subclinical atherosclerosis in our Finnish cohort. PROCAM risk score included regional adjustment factors due to geographical differences in prevalence of CHD(11). However, PROCAM displayed similar performance as Framingham risk score. Seemingly, nationality had little interfering effect on risk estimation in our analyses.

LIMITATIONS

Risk scores were originally designed for prediction of myocardial infarction or coronary heart disease death over a 10-year period(8,17,18) apart from Reynolds which predicts 10-year cardiovascular event risk(9,10). Data on CVD end-points was unavailable in our cohort aged 30–45 years. Instead, we used markers of subclinical atherosclerosis, i.e. high carotid IMT, low carotid distensibility and low brachial FMD in 2007 follow-up study as outcome variables. Of these, most consistent data concerning associations with CVD events is available on IMT. In a review by Lorenz et al.(27), it was shown that IMT is a strong predictor of CVD events independent of conventional risk factors. However, in the Rotterdam study(28) IMT measurements did not statistically significantly improve predictive value when added to conventional risk factor data. Reynolds risk score for females included hemoglobinA_{1C} levels for diabetics. However, hemoglobinA_{1C} was not measured in Young Finns study and thus, effect of diabetes was omitted from analyses. Effect of exclusion, if anything, is likely to be small due to the number of diabetic men and (N=6 in 2001 and N=11 in 2007). In addition, Reynolds and PROCAM risk scores included myocardial infarction <60 years in either parent as parental history of CVD. In Young Finns, parental history of CVD was classified as myocardial infarction <55 years in either parent in 2001 and <55 years in males and <65 years in females in 2007.

CLINICAL IMPLICATIONS

CVD risk scores are able to predict future subclinical atherosclerosis in young adults. According to our results, risk of subclinical atherosclerosis in young adults can be assessed with any of the examined risk scores. Since our findings link early adulthood CVD risk to vascular changes, young adults should be motivated to reduce CVD risk at an early stage.

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Figure 1a.

Figure 1b.

Figure 1.

Distribution of 10-year risk of CHD event (Framingham, SCORE and Finrisk) or CVD event (Reynolds) in (a) females and (b) males in 2001.

Table 1

Descriptive data in 2001 and 2007.

Year 2001	Men	Women
N	794	1015
Age (years)	31.9	31.9
BMI (kg/m ²)	25.7±4.0	24.4±4.5
SBP (mmHg)	121±12	112±12
DBP (mmHg)	73±11	69±10
Total cholesterol (mmol/l)	5.19±0.95	5.08±0.93
LDL-cholesterol (mmol/l)	3.43±0.92	3.16±0.76
HDL-cholesterol (mmol/l)	1.15±0.27	1.41±0.31
Triglycerides (mmol/l)	1.50±0.95	1.17±0.69
C-reactive protein (mg/l)	1.45±3.31	2.25±4.42
Smokers (N)	209 (26.3%)	177 (17.4%)
Diabetics (N)	6 (0.8%)	6 (0.6%)
Family history of CVD (N)	76 (9.6%)	86 (8.5%)
IMT (mm)	0.59±0.10	0.57±0.08
CDist (%/ 10mmHg)	2.33±0.66	2.00±0.77
FMD (%)	6.84±4.04	8.78±4.50
Framingham (%)	2.53±2.65	1.00±1.02
SCORE (%)	0.22±0.25	0.02±0.02
Finrisk (%)	0.91±0.81	0.41±0.25
PROCAM (%)	1.69±2.31	0.12±0.13
Reynolds (%)	0.66±0.62	0.21±0.19
Year 2007	Men	Women
N	794	1015
Age (years)	37.9	37.9
BMI (kg/m ²)	26.7±4.2	25.3±4.9
SBP (mmHg)	126±13	116±14
DBP (mmHg)	79±11	73±11
Total cholesterol (mmol/l)	5.19±0.95	4.94±0.86
LDL-cholesterol (mmol/l)	3.28±0.82	2.96±0.72
HDL-cholesterol (mmol/l)	1.21±0.28	1.45±0.33
Triglycerides (mmol/l)	1.63±1.05	1.18±0.63
C-reactive protein (mg/l)	1.48±2.63	2.02±3.56
Smokers (N)	167 (21.1%)	150 (14.9%)
Diabetics (N)	12 (1.5%)	11 (1.1%)
Family history of CVD (N)	76 (9.6%)	86 (8.5%)
IMT (mm)	0.64±0.11	0.61±0.09
CDist (%/ 10mmHg)	1.73±0.61	2.03±0.73
FMD (%)	7.44±3.71	9.84±4.83

Year 2001	Men	Women
Framingham (%)	4.73±4.00	1.94±1.78
SCORE (%)	0.57±0.53	0.07±0.08
Finrisk (%)	1.56±1.23	0.64±0.41
PROCAM (%)	2.59±2.96	0.20±0.23
Reynolds (%)	1.37±1.11	0.34±0.31

Data are mean±SD for continuous variables or N (%) for dichotomous variables.

Table 2

Spearman's correlation between 10-year CVD risk scores and ultrasound measurements.

Firisk	0.30***	0.37***	0.39***	-0.33***	-0.25***	-0.25***	0.02	-0.02	-0.008
SCORE	0.33***	0.38***	0.40***	-0.34***	-0.26***	-0.26***	0.01	-0.05	-0.02
Reynolds	0.35***	0.40***	0.42***	-0.39***	-0.28***	-0.28***	0.01	-0.03	-0.02
PROCAM	0.27***	0.33***	0.38***	-0.31***	-0.22***	-0.23***	0.02	-0.01	0.006
Women	2001-2001	2007-2007	2001-2007	2001-2001	2007-2007	2001-2007	2001-2001	2007-2007	2001-2007
Framingham	0.29***	0.39***	0.35***	-0.33***	-0.31***	-0.30***	0.07*	0.002	-0.04
Firisk	0.28***	0.38***	0.32***	-0.24***	-0.25***	-0.24***	0.04	-0.01	-0.04
SCORE	0.32***	0.37***	0.35***	-0.31***	-0.33***	-0.32***	0.05	-0.03	-0.07*
Reynolds	0.26***	0.38***	0.32***	-0.34***	-0.32***	-0.27***	0.09**	0.03	-0.002
PROCAM	0.28***	0.39***	0.32***	-0.27***	-0.27***	-0.24***	0.08**	0.02	-0.02

2001-2001 = correlation between CVD risk score in 2001 and ultrasound measurement in 2001.

2007-2007 = correlation between CVD risk score in 2001 and ultrasound measurement in 2007.

2007-2007 = correlation between CVD risk score in 2007 and ultrasound measurement in 2007.

Model fit, discrimination, calibration, and reclassification indices for prediction of 6-year subclinical outcomes from year 2001 risk scores.

Table 3

Outcome	Framingham		Finnrisk		SCORE		PROCAM		Reynolds	
	Statistic	P-value*	Statistic	P-value*	Statistic	P-value*	Statistic	P-value*	Statistic	P-value*
High carotid IMT (>90 th percentile) or plaque										
OR	1.7	1.7	1.7	***	1.7	***	1.5	***	1.7	***
(95%CI) [†]	(1.5–2.0)	(1.5–2.0)	(1.5–2.0)	(1.5–1.9)	(1.5–1.9)	(1.5–1.7)	(1.3–1.7)	(1.5–1.9)	(1.5–1.9)	
AUC	0.728	0.733	0.41	0.726	0.83	0.712	0.15	0.729	0.95	
(95%CI)	(0.698–0.758)	(0.702–0.763)		(0.695–0.757)		(0.681–0.744)		(0.698–0.759)		
H-L	51.3	60.6	***	54.7	***	57.2	***	46.3	***	
NRI	-	2.2%	0.25	3.7%	0.18	-4.9%	0.12	3.9%	0.16	
IDI	-	-0.17%	0.29	-0.90%	0.02	-2.76%	<0.01	-0.10%	0.41	
Low CDist (<10 th percentile)										
OR	1.4	1.3	***	1.3	***	1.2	***	1.4	***	
(95%CI) [†]	(1.2–1.5)	(1.2–1.5)	(1.2–1.5)	(1.1–1.4)	(1.1–1.4)	(1.1–1.4)		(1.3–1.6)		
AUC	0.652	0.652	0.97	0.642	0.45	0.639	0.41	0.658	0.54	
(95%CI)	(0.612–0.692)	(0.611–0.693)		(0.603–0.681)		(0.598–0.680)		(0.618–0.697)		
H-L	25.8	29.9	***	27.8	***	27.2	***	25.1	***	
NRI	-	1.9%	0.32	-3.8%	0.22	-27.4%	<0.01	6.9%	0.04	
IDI	-	-0.05%	0.42	-0.50%	0.005	-0.75%	0.01	0.78%	0.003	
Low brachial FMD (<10 th percentile)										
OR	1.2	1.2	***	1.2	***	1.1	***	1.2	***	
(95%CI) [†]	(1.1–1.4)	(1.1–1.4)	(1.1–1.4)	(1.1–1.4)	(1.1–1.4)	(1.0–1.3)		(1.1–1.4)		
AUC	0.568	0.578	0.13	0.596	<0.05	0.594	0.08	0.582	0.09	
(95%CI)	(0.521–0.615)	(0.531–0.624)		(0.550–0.642)		(0.548–0.639)		(0.535–0.629)		
H-L	4.4	8.0	***	18.7	***	19.1	***	8.8	***	

Outcome	Framingham		Fimrisk		SCORE		PROCAM		Reynolds	
	Statistic	Statistic	Statistic	P-value*	Statistic	P-value*	Statistic	P-value*	Statistic	P-value*
NRI	-	-1.5%	0.35	0.10	-7.1%	0.10	-13.6%	<0.01	5.1%	0.08
IDI	-	-0.29%	0.01	0.10	-0.22%	0.10	-0.50%	<0.01	-0.08%	0.27

* P-values for comparisons between Framingham (reference risk score) vs. each of Fimrisk, SCORE, PROCAM, or Reynolds risk scores.

† Odd ratios are expressed for a 1 standard deviation increase in Framingham, Fimrisk, SCORE, PROCAM, or Reynolds risk scores.

Analyses for each outcome were limited to subjects that had sufficient risk variables to calculate all risk scores (IMT, N = 1761; CDist, N = 1754; FMD, N = 1751).

Abbreviations. AUC = area under receiver-operating characteristic curve; CDist = carotid artery distensibility; CI = confidence interval; FMD = flow-mediated dilatation; H-L = Hosmer-Lemeshow chi-square statistic; IMT = intima-media thickness; NRI = Net reclassification improvement; OR = odds ratio; IDI = integrated discrimination improvement.

Note.

Population mean for high IMT/plaque = 15.5%. Risk categories, of <14%, 14–16%, 16–20%, ≥20% used for calculation of NRI

Population mean for low CDist = 10.2%. Risk categories, of <9%, 9–11%, 11–15%, ≥15% used for calculation of NRI

Population mean for low FMD = 10.3%. Risk categories, of <9%, 9–11%, 11–15%, ≥15% used for calculation of NRI