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QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES

State-of-the-Art Paper

Value and Limitations of Existing Scores for the Assessment of Cardiovascular Risk

A Review for Clinicians

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Atherosclerotic cardiovascular diseases (CVDs) are the biggest causes of death worldwide. In most people, CVD is the product of a number of causal risk factors. Several seemingly modest risk factors may, in combination, result in a much higher risk than an impressively raised single factor. For this reason, risk estimation systems have been developed to assist clinicians to assess the effects of risk factor combinations in planning management strategies. In this article, the performances of the major risk estimation systems are reviewed. Most perform usably well in populations that are similar to the one used to derive the system, and in other populations if calibrated to allow for different CVD mortality rates and different risk factor distributions. The effect of adding "new" risk factors to age, sex, smoking, lipid status, and blood pressure is usually small, but may help to appropriately reclassify some of those patients who are close to a treatment threshold to a more correct "treat/do not treat" category. Risk estimation in the young and old needs more research. Quantification of the hoped-for benefits of the multiple risk estimation approach in terms of improved outcomes is still needed. But, it is likely that the widespread use of such an approach will help to address the issues of both undertreatment and overtreatment. (J Am Coll Cardiol 2009;54:1209–27) © 2009 by the American College of Cardiology Foundation

Atherosclerotic cardiovascular diseases (CVDs) are the biggest causes of death worldwide (1). Decades of research have determined that atherosclerosis develops insidiously, is often advanced by the time that symptoms occur, but may then kill rapidly. It follows that treatments may be inapplicable if the person dies rapidly, or palliative even if they survive long enough to reach medical care (2). While this is not to gainsay the wonderful advances in therapy that have occurred, it is clearly desirable to determine the causes of CVD and to see if such knowledge can translate into effective preventive strategies.

In this review, we define the term "risk factor" and outline the concept of and rationale for total risk estimation. The characteristics of a clinically useful risk estimation system are tabulated. Current risk estimation systems are described and compared. Substantial limitations are common to all risk estimation systems, and we describe these and outline what is being done to deal with them, including recalibration, the effect of incorporating newer risk factors, and the challenges of risk estimation in the young and the old. We conclude by looking at the evidence—or lack of it—that a total risk estimation approach is likely to improve outcome.

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Total CVD Risk Assessment

A century of intensive research has taught us that the mass occurrence of CVD relates to interlocking genetic, social, physiological, and environmental factors. A comprehensive approach to prevention would address all of these. While awaiting major advances in genetics and the ability to reduce social inequalities, it has become evident that certain factors actually cause atherosclerosis, and that their modification can reduce mortality—especially with regard to smoking cessation and the effective control of blood pressure and blood cholesterol.

A risk factor may be defined as a characteristic of a person that is associated with an increased risk of developing a specific disease such as atherosclerotic CVD. To be clinically relevant, it should be accepted as causal (3) and modifiable, and a defined benefit should result from such modification. Most risk estimation systems include age, sex, smoking, blood lipids, and blood pressure as their core variables. In this context, age is a measure of exposure time and not a risk factor as such.

The term "total risk estimation" is perhaps a misnomer, as no risk estimation system accommodates all known risk

Abbreviations and Acronyms

AUROC = area under the receiver-operating characteristic curve
CHD = coronary heart disease
CRP = C-reactive protein
CVD = cardiovascular disease
NRI = net reclassification index

factors. However, it refers to the fact that CVD, in most people, is the product of several risk factors that may interact to greatly increase risk, and an approach that focuses on single risk factors may result in inappropriate management decisions. Looking at Table 1, taken from the current Joint European Guidelines on the prevention of CVD in clinical practice (2), who should receive the statin? The 60-year-old woman with a blood cholesterol level of 8 mmol/l (309 mg/dl) and a 2% 10-year risk of fatal CVD, or the man of the same age with a cholesterol of 5 mmol/l (193 mg/dl) but a 10-fold higher risk because of multiple other risk factors? Current therapeutic trial data do not tell us, but logic would suggest the man, along with, of course, attention to all other factors.

These considerations have led the authors of all current guidelines to stress the need to consider the likely impact of all risk factors before making clinical management decisions and, in most cases, to recommend a system of evaluating combined risk factor effects (2,4–6).

In regard to risk estimation and management, McGorrian et al. (7) define 4 challenges that face the busy health professional: 1) How do I identify people who are at increased risk of a cardiovascular event? 2) How do I weight the individual effects of all the causative risk factors when assessing a person's risk? 3) How do I stratify that risk to determine who needs lifestyle advice and who needs additional medical therapy? 4) How do I ensure that I am not overmedicalizing those persons who are at low risk of an event?

Risk estimation systems provide some tools that may assist the health care professional. The criteria for a clinically useful risk estimation system are outlined in Table 2.

Current Risk Estimation Systems

Many risk estimations systems are in existence (8–14). The best known and probably the most widely used, globally, is the Framingham risk score (8). The Framingham group also pioneered many of the methods commonly used in risk estimation (15,16). Several modified versions of the Framingham function have also been developed and presented as either charts or tables and have been included in national and international guidelines (17,18). Table 3 details the characteristics of the Framingham function and allows comparison with some other commonly used systems. Recently, several other systems have been introduced offering advantages in terms of inclusion of extra risk factors, and so forth. However, in this review, we have concentrated mainly on those systems that are recommended by guidelines on CVD prevention (8–14). Most current risk estimation systems calculate the absolute risk of CVD events; that is logical but can be problematic for younger people. This issue is addressed fully in the "Risk Estimation in Younger Persons" section in the following text.

The risk estimation systems will be compared based on the characteristics that we consider to be important for risk estimation systems, as detailed in Table 2.

Methods

The Framingham and the ASSIGN scoring systems are based on intermediate-sized samples that are representative of the general population (8,10). The PROCAM (Prospective Cardiovascular Münster) study is based on a sample of industrial employees (12); it may be considered somewhat underpowered for risk estimation for women (49 events). The SCORE (Systematic COronary Risk Evaluation) system is based on a substantially larger dataset that contains >205,000 persons, representing 2.1 million person-years of observation (9). Because it is a pooled dataset of 12 European prospective studies, it has the potential to accommodate more of the heterogeneity across Europe in terms of baseline CVD risk. The majority of the included studies are representative of the general population, although in the lower-risk European countries, some occupational cohorts were also included (9).

The QRISK (19) and QRISK2 (11) systems are different because they are based on databases of general practice attendees and are, therefore, not random representative samples of the population; additionally, the baseline risk factor measurements would have been obtained at varying times during the observation period, methods were not standardized, and there are substantial amounts of missing data, which were imputed as part of the analysis. However, the advantage of using these data is the substantially larger numbers that can be included; QRISK2 included >1.5 million people (11). Additionally, these systems, based on general practice registers, have the potential for ongoing

Table 1 Impact of Combinations of Risk Factors on Total CVD Risk

Sex	Age (Yrs)	Total Cholesterol, mmol/l (mg/dl)	SBP (mm Hg)	Current Smoker	SCORE Risk (% 10-Yr Risk of Fatal CVD)
Female	60	8 (309)	120	No	2
Female	60	7 (271)	140	Yes	5
Male	60	6 (232)	160	No	8
Male	60	5 (193)	180	Yes	21

CVD = cardiovascular disease; SBP = systolic blood pressure; SCORE = Systematic COronary Risk Evaluation.

Table 2 Criteria for a Clinically Useful Risk Estimation System

Appropriate statistical methods for derivation of the function
Representative sample from the population from which the system is to be applied
Sufficient power (large enough sample size)
Accepted statistical methods
The end point predicted by the function should be defined in such a way that it is easily standardized across populations and relevant to the outcomes of randomized controlled trials of preventive measures
Performance of the function—internal and external validity
Discrimination: the ability of the function to separate those who will develop the end point from those who will not. Often assessed using:
Area under receiver operating characteristic curve (AUROC)—a means for expressing the maximum achievable sensitivity and specificity. An AUROC of 1 indicates perfect discrimination; 0.5 equates to chance. Values in the region of 0.9 are often achieved for diagnostic tests. Values rarely exceed 0.8 for risk estimation. Harrell's C statistic gives the same information but can be used with variable follow-up.
Sensitivity/specificity/positive predictive value/negative predictive value
Calibration—a measure of how closely predicted outcomes agree with actual outcomes. Often assessed using either:
Hosmer-Lemeshow goodness of fit testing—lower values indicate better fit, values <20 generally considered good fit. Significant p values indicate lack of fit.
Predicted to observed ratios—the closer the value to 1, the better the fit. Values >1 indicate overestimation and vice versa.
Reclassification
Net reclassification index—a measure of the net percentage of those who do and who not develop the end point within the time period that are correctly reclassified to a different risk category when a new risk factor is added to the risk estimation system.
Usability of the system
The format affects the ease of use of the system. This will also impact on the uptake of the system by users.
Inclusion of appropriate risk factors
Most risk estimation systems include age, sex and conventional risk factors including lipid levels, smoking, and blood pressure.
Inclusion of other factors may be important, especially if they have been shown to be powerful risk determinations and prevalent in the population to which to system is to be applied (e.g., social deprivation).
Some advocate the use of only risk factors that are potentially modifiable, although most agree that risk factors to be included should be chosen based on whether they improve risk estimation because those identified as high risk can still modify their risk by favorably altering their other risk factors.
Systems using only easily measured non–laboratory measures have been developed recently.
Has use of the system been shown to result in measurable health gains?

revisions utilizing newer data (36,37). The Reynolds risk scores use a different approach again; these scores, which have been derived separately for men and women, are based on the prospective follow-up of 2 separate randomized controlled trials (20,21).

The choice of end point predicted by the function is also a consideration. Early systems usually estimated coronary heart disease (CHD) risk (16). Because atherosclerosis may manifest elsewhere, for example, as stroke or peripheral vascular disease, more recent systems have tended to use total CVD as the primary end point (8,9). It is, however, helpful to retain the capacity to estimate risk of cause-specific events, because stroke, for example, may be proportionately more common in certain populations such as low-risk countries and older persons (38).

The end point should be as clearly defined as possible to prevent coding difficulties when the function is applied to external populations. This was a problem with initial versions of the Framingham function, which included "softer" end points, including onset of angina of effort and silent myocardial infarctions based on electrocardiographic re-examinations (15). Additionally, this end point did not correspond to the end points used in clinical trials. More recent versions have been based solely on "harder" end points (8) or have allowed an option for calculation of risk of harder end points (16). The SCORE system estimates risk of fatal CVD events only, whereas the other systems in Table 3 estimate risk of CHD/CVD events (9). Some consider this a disadvantage; however, this very clear end point definition was specifically chosen because it was subject to less variation in terms of coding and end point ascertainment when being applied across 12 different cohort studies (9). The ease of application of this definition also aids the recalibration process, as will be discussed in the following text.

Statistical Considerations

Most of the current risk estimation systems are based on proportional hazards models—either Cox (semiparametric) (8,10,11,20,21) or Weibull (parametric) (9,12). Logistic regression had been used previously, but these newer methods afforded the advantage of allowing for losses to follow-up and variable observation time within the cohort. The Cox method has the advantage of not making any assumptions regarding the shape of the underlying survival, in contrast to the Weibull method, which imposes a parametric function on the baseline survival. Weibull was chosen for the original SCORE function and age was included as part of the time variable, as opposed to as a risk factor, which allowed the effect of age to vary at different ages (9). This method also makes more efficient use of the data by allowing risk to be estimated for periods greater than the length of the study's follow-up (9). This advantage of

Table 3 Characteristics of Current Risk Estimation Systems (WHO/ISH)

	Framingham (8)	SCORE (9)	ASSIGN – SCORE (10)	QRISK1 (19) and QRISK2 (11)	PROCAM (12)	WHO/ISH (14)	Reynolds Risk Score (20,21)
Data	Prospective studies: Framingham Heart Study and Framingham Offspring Study Latest version includes both	12 pooled prospective studies from 11 European countries	SHHEC prospective study	QRESEARCH database	Prospective study	Methods differ to other risk estimation functions—not based on prospective data	Randomized controlled trials Women: Women's Health Study Men: Physician's Health Study II
Population and sample type	General population, Framingham, Mass, U.S. Volunteer	Mostly random samples from general population, some occupational cohorts	Random sample from general population in Scotland	Health records of general practice attendees—not random	Healthy employees Volunteer—not random	Not applicable	Women: Health Service employees Men: Physicians Volunteer—not random
Baseline of data	Baselines: 1968–1971, 1971–1975, 1984–1987	Baselines: 1972–1991	Baseline: 1984–1987	Baseline: 1993–2008	Baseline: 1978–1995		Women baseline: 1993–1996 Men baseline: 1997
Sample size	3,969 men and 4.522 women	117,098 men and 88,080 women	6,540 men and 6,757 women	1.28 million (QRISK1) 2.29 million (QRISK2)	18,460 men and 8,515 women	Not applicable	24,558 women and 10,724 men
Statistical methods	Cox (Weibull—earlier versions) (15)	Cox and Weibull	Cox	Imputation of substantial missing data Cox	Cox and Weibull Exploratory analyses with neural networks also (22)	Relative risks associated with risk factors were taken from comparative risk assessment project; these were combined with estimated absolute risks for each WHO subregion based on global burden of disease study	Cox
Calculates	10-yr risk of CHD events originally Latest version: 10-year risk of CVD events Risk age	10-yr risk of CVD mortality	10-yr risk of CVD events	10-yr risk of CVD events	2 separate scores calculate 10-yr risks of major coronary events and cerebral ischemic events	10-yr risk of CVD events	10-yr risk of incident myocardial infarction, stroke, coronary revascularization, or cardiovascular death
Age range	30–75 yrs	40–65 yrs	30–74 yrs	35–74 yrs	20–75 yrs	40–79 yrs	45–80 yrs
Variables	Sex, age, total cholesterol, HDL cholesterol, SBP, smoking status, diabetes, hypertensive treatment	Sex, age, total cholesterol or total cholesterol/HDL cholesterol ratio, SBP, smoking status Versions for use in high- and low-risk countries	Sex, age, total cholesterol, HDL cholesterol, SBP, Smoking—no. of cigarettes, diabetes, area-based index of deprivation, family history of CHD	QRISK1—sex, age, total cholesterol to HDL cholesterol ratio, SBP, smoking status, diabetes, area-based index of deprivation, family history, BMI, antihypertensive treatment QRISK2—also includes ethnicity and chronic diseases	Age, sex, LDL cholesterol, HDL cholesterol, diabetes, smoking, SBP	Sex, age, SBP, smoking status, diabetes ± total cholesterol; different charts available for worldwide regions	Sex, age, SBP, smoking, hsCRP, total cholesterol, HDL cholesterol, family history of premature MI (parent age <60 yrs), HbA1C if diabetic
Formats	Simplified scoring sheets; color charts have been generated for some guidelines (e.g., JBS and New Zealand guidelines); online calculators; portable calculators	Color-coded charts, Heart Score—online and CD-based stand-alone electronic versions	Online calculator	Online calculator	Simple scoring sheet and online calculators	Color-coded charts	Online calculator

Continued on next page

Table 3 Continued

	Framingham (8)	SCORE (9)	ASSIGN – SCORE (10)	QRISK1 (19) & QRISK2 (11)	PROCAM (12)	WHO/ISH (14)	Reynolds Risk Score (20,21)
Developments	Latest version includes version based on non-laboratory values only, substituting BMI from lipid measurements	National, updated recalibrations	—	QRISK2 includes interaction terms to adjust for the interactions between age and some of the variables	Recent change in the methods (Weibull) allows allows extension of risk estimation to women and broader age range	—	—
Recommended by guidelines	NCEP guidelines (23), other national guidelines recommend adapted versions, including New Zealand (18)	European guidelines on CVD prevention (2)	Recommended by SIGN (Scottish Intercollegiate Guidelines Network) (24)	NICE guidelines on lipid modification (25)	International Task Force for Prevention of Coronary Disease guidelines	WHO guidelines on CVD prevention (14)	No
Website	Online and downloadable risk calculator available at: www.nhlbi.nih.gov/guidelines/cholesterol/index/htm	Online and downloadable risk calculators available at: www.heartscore.org	Online risk calculator available at: www.assign-score.com	Online risk calculator available at: www.qrisk.co.uk	Online calculator available at: www.chd-taskforce.com/calculator	Charts downloadable at: www.who.int/cardiovascular_diseases/guidelines/Pocket_GL_information/en/index.html	Online calculator: www.reynoldsriskscore.com
Internal validation—discrimination	AUROC men: 0.76 (0.75 to 0.78) AUROC women: 0.79 (0.77 to 0.81)	AUROC high risk: 0.80 (0.80 to 0.82) AUROC low risk: 0.75 (0.73 to 0.77)	AUROC men: 0.73 AUROC women: 0.77	QRISK2: AUROC men: 0.79 (0.79 to 0.79) AUROC women: 0.82 (0.81 to 0.82)	AUROC 0.82 for coronary events AUROC 0.78 for cerebral ischemic events	Not specified	AUROC women: 0.808 AUROC men: 0.708
Internal validation—calibration	HL men: 13.48 HL women: 7.79	Not specified	Observed 10-year CVD incidence rates men: 11.7%; women 6.4% Median ASSIGN men: 11.7%; women: 6.2%	Good correlation between observed and predicted risks in both men and women—presented graphically only— each decile of risk	Not specified	Not specified	HL women: 0.62 HL men: 12.9
External validation—discrimination	PRIME study Belfast: 0.68 (26) PRIME study France: 0.66 (26) Dutch study: 0.86 (0.84 to 0.88) (27) Cleveland study: 0.57 (28) China: men 0.75 (0.72 to 0.78) (29); China: women 0.79 (0.74 to 0.85) (29) THIN (UK): men 0.74 (0.73 to 0.74) (30); women 0.76 (0.76 to 0.76) (30) EPIC Norfolk: 0.71 (31) UK women (BHHS): 0.66 (0.62 to 0.69) (32)	Dutch study: 0.85 (0.83 to 0.87) (27) Cleveland study: 0.73 (28) Norwegian study: range for different age groups: men 0.65 to 0.68 (33); women 0.66 to 0.72 (33) Austrian study: men 0.76 (0.74 to 0.79) (34); women 0.78 (0.74 to 0.82) (34) Icelandic study: 0.80 (0.78 to 0.82)—SCORE high (35); 0.80 (0.77 to 0.82)—SCORE low (35)	Not assessed	THIN database (UK): QRISK1: AUROC men: 0.76 (0.76 to 0.77) (30) AUROC women: 0.79 (0.79 to 0.79) (30)	PRIME study Belfast: 0.61 (26) PRIME study France: 0.64 (26)	Not assessed	Not assessed

AUROC = area under receiver operating characteristic curve; BMI = body mass index; CHD = coronary heart disease; CRP = C-reactive protein; CVD = cardiovascular disease; Hb = hemoglobin; HDL = high-density lipoprotein; HL = Hosmer Lemeshow; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MI = myocardial infarction; SBP = systolic blood pressure; WHO/ISH = World Health Organization/International Society of Hypertension.

the Weibull model was also utilized in the most recent version of the PROCAM system to allow a function to be derived in women—for whom limited data were available (12). However, as demonstrated by the both the PROCAM and SCORE groups, the choice of Cox or Weibull makes little practical difference to risk estimation.

Other more complicated methods also exist, including cluster analysis, tree-structured analysis, and neural networks (39). These methods are particularly useful for selecting the most appropriate variables when a large number of potential predictors of risk are available. Neural networks do not assume that risk factors function in a constant and continuous fashion and can account for complex nonlinear relationships and interactions between risk factors (22). Cluster analysis focuses on the identification of groups of persons with similar risk factor characteristics who have similar levels of risk. However, there is difficulty in obtaining large epidemiological datasets with extensive numbers of predictor variables available. Additionally, the necessity for measurement of multiple factors in clinical practice adds to complexity and is, therefore, likely to limit clinical usage of these systems. Tree-structured systems attempt to progressively split the population into smaller subgroups, through sequential introduction of the risk factors, starting with the simplest. The advantage is that some persons can be classified as high or low risk based on very few risk factors, reducing unnecessary laboratory testing for them. The main problem with all of these methods is model shrinkage—their predictive ability declines sharply once the model is applied to an external dataset, which limits their utility in clinical practice (39).

The WHO/ISH (World Health Organization/International Society of Hypertension) risk prediction charts offer an advantage in that they have been developed for each specific WHO subregion (14). The disadvantage is the methodology. Only a limited description of the methods has been provided (14). This specifies that the charts were developed by creating a hypothetical dataset for each region—on the basis of the risk factor prevalence in that area, using the mean and standard deviation of risk factor levels measured as part of the collaborative risk assessment study (40). Each person was then assigned a relative risk, based on the combination of his or her risk factor level and the relative risk associated with each risk factor, as estimated from mainly prospective studies. The relative risk for each person was then scaled according to the baseline risk in that region, as estimated from the global burden of disease study, in order to estimate the absolute risk. These methods require substantial further investigation to determine accuracy and validity, as acknowledged by the authors (14).

Performance: Internal and External Validation

The main ways to describe the performance of a risk estimation system are discrimination, calibration, and reclassification. These are explained in Table 2.

Internal validation. The assessment of model performance in the dataset from which it was derived, internal validation, is important in checking the mathematical performance of the model used and appropriate fit of the model. As shown in Table 3, risk estimations systems generally perform well when assessed in this way (8–12,20,21). However, the derivation dataset (or a proportion of the same dataset from which the derivation dataset was drawn) is distinctly limited in terms of comparing one function with another. These methods will be inherently biased toward the new function. That occurs not only because the exact baseline survival of the population is included in the new function, but also because the new function has been derived for prediction of the exact end point in the test dataset, and identical risk factor definitions are used in the test and derivation datasets. Therefore, assertions of superiority of new functions when assessed using the derivation dataset of the new function should be viewed with caution (10,11). Comparing the performance of functions in an external dataset is more appropriate.

External validation. External validation of the Framingham function has been assessed in numerous studies (26–32). Most external validation exercises were based on either the 1991 function of Anderson et al. (15) or the 1998 function of Wilson et al. (16) that assessed risk of CHD events, as opposed to the 2008 function by D'Agostino et al. (8) that estimates risk of CVD incidence. In general, external validations of Framingham functions have demonstrated good discrimination, with area under the receiver-operating characteristic curve (AUROCs) or C-statistics ranging from 0.66 to 0.88, as shown in Table 3, with some exceptions (28,41). These have generally been higher in women. The discrimination in the elderly has been poorer, as will be as discussed in following text (41).

Some external validation studies have shown poor discrimination with the Framingham function. That may be due to a narrow age range (41), which does not allow for the predictive ability of age as a risk factor or differences in end point definition. For example, the study by Aktas et al. (28) showed SCORE to be a stronger predictor of CVD mortality than the Framingham function; however, the Framingham function used was intended to estimate risk of CHD events, not mortality (28). Likewise, the low AUROCs of the Framingham function in the PRIME study (26) may have been related to differences in ascertainment of end points in the 2 studies because earlier versions of the Framingham function included angina and silent myocardial infarctions (42). The SCORE system has been externally validated in a number of studies, yielding results similar to Framingham, as shown in Table 3. The QRISK system performed well when externally validated in the UK THIN (The Health Improvement Network) GP register (30). Experience of the external validity of PROCAM is more limited (12). The ASSIGN-SCORE, QRISK2, and the WHO/ISH investigators have not yet reported any studies of external validation.

Jackson (43) has drawn attention to the fact that, because in clinical practice a threshold is used for defining high/low risk and treatment decisions are based around this, it is important, in addition to reporting these measures of summary discrimination (AUROC and C-statistic), to consider the discrimination at the threshold of high/low risk. For example, for the SCORE function, the authors report the sensitivity and specificity of the function at a variety of cut-points for the threshold for high or low risk (9).

Calibration. Calibration measures the agreement between the observed and predicted. As demonstrated by Diamond (44), it is not possible to have a system with both perfect calibration and discrimination. There is an inherent trade-off between the 2. They demonstrated a discrimination of 83% (AUROC) in a modelling exercise, when the function was perfectly calibrated (44).

Risk estimation systems also change how well calibrated they are with time and place. Differences in the baseline rates of CVD in different geographic regions mean that risk estimation systems that are well calibrated in one region will lead to overestimation or underestimation of risk in another (45). Likewise, secular changes in the incidence of CVD over time mean that risk estimation systems become outdated. For example, in most of the developed world, CVD incidence is now decreasing (13,46). That means that over time, risk estimation systems will start to overestimate risk. Conversely, in areas where CVD rates are still increasing, current risk estimation systems will underestimate risk. The CHD mortality trends for men across time and place are illustrated in Figure 1.

A systematic review by Brindle et al. (45) (Fig. 2) demonstrated the calibration of the Framingham function in several different cohorts. The function overestimated risk in cohorts for which the baseline risk was lower than that of the Framingham cohort, for example, cohorts in France and Germany. The risk was underestimated in cohorts with a worse baseline survival, for example, cohorts of diabetic patients or patients with a family history of CHD. Good calibration was demonstrated in cohorts that had similar baseline CHD rates to Framingham at that time.

Risk functions can, however, be recalibrated to overcome this problem. This recalibration process will be discussed in the section on advances in risk estimation.

The net reclassification index is a novel method for assessing reclassification into more appropriate risk categories using new risk functions and is discussed in the following text.

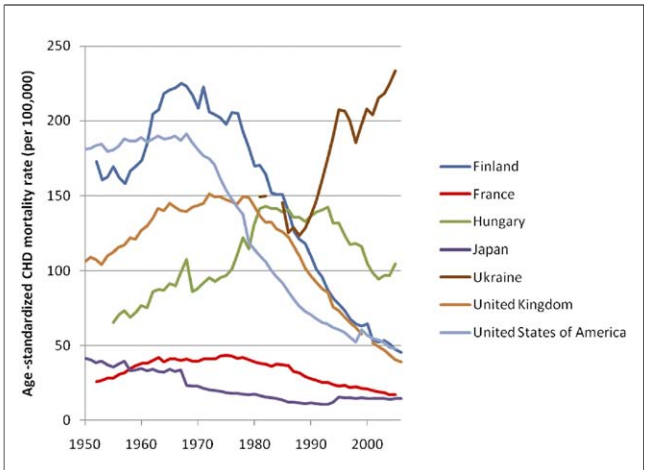


Figure 1 **CHD Mortality Rates in Men <65 Years Old**

Global age-standardized coronary heart disease (CHD) mortality rates in men under age 65 years (1950 to 2006). Figure drawn using World Health Organization statistics (13). **Dark blue line** indicates Finland; **red line**, France; **green line**, Hungary; **purple line**, Japan; **dark red line**, Ukraine; **orange line**, United Kingdom; **light blue line**, U.S.

Usability, Inclusion of Appropriate Risk Factors, and Effect of Risk Estimation on Clinical Outcomes

Risk estimation systems are of little value unless clinicians actually use them in day-to-day practice. Previous studies have shown that the format of the system affects the usage of risk estimation systems and the accuracy with which clinicians use them (47). For example, simplifier color charts were shown to be preferred to more complicated numerical tables (47). The SCORE chart (9), shown in Figure 3, is a good example of a simple, easy to use risk chart. The SCORE investigators acknowledge that the format of the SCORE charts is based on that of the original New Zealand risk charts used in their guidelines (18). Some other formats of current risk estimation systems are shown in Figure 4.

In general, electronic systems should be user friendly, especially because previous studies have shown that health care providers are less likely to use computerized systems, compared with simpler paper charts, even after training (49). An innovative solution to improving usability is the integration of the risk estimation system with the GP database. In this way, the risk estimate is automatically calculated. The PREDICT-CVD system, an integrated system developed to aid implementation of the New Zealand, resulted in a 4-fold increase in the rate of documentation of risk estimates in the medical notes (50).

The risk chart format has several advantages in that it is easy to use and inexpensive to produce. The SCORE chart combines ease of use and accuracy because the integer value for the risk is displayed as well as the color-coded risk category. Previous studies have shown inaccuracy of risk estimates when color-coded charts alone are used (25). The weakness of the paper chart is that only a limited number of variables can be incorporated.

Most of the current risk estimation systems include the conventional risk factors: age, sex, smoking, blood pressure, and lipid levels. Recently, there has also been increasing interest in the inclusion of family history of CHD (10, 19–21), social deprivation measures (10,19), ethnicity (11), and interaction variables that adjust for the use of antihypertensive medication (10,16,19). Inclusions such as social

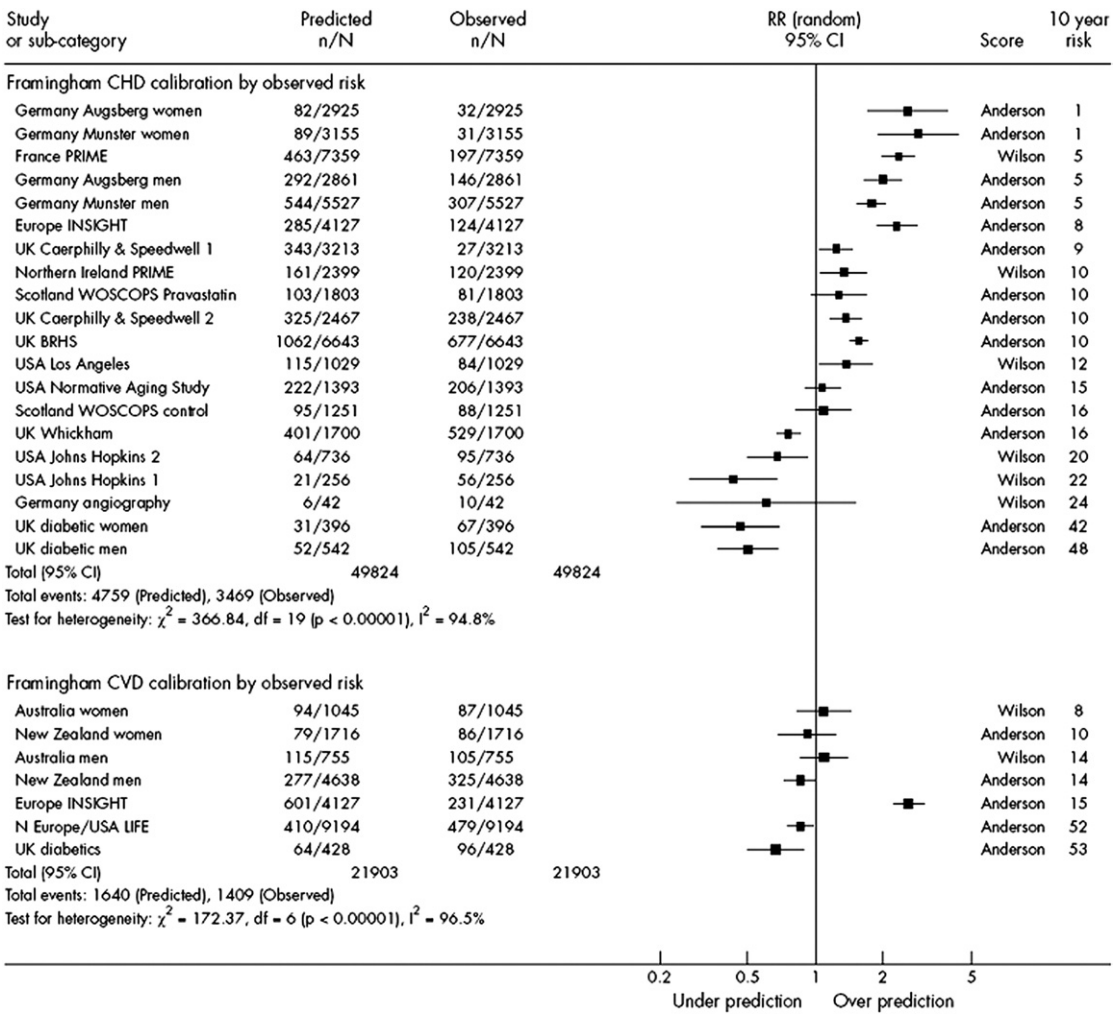


Figure 2 **Observed to Predicted Risk**

Observed to predicted risk demonstrated in external validation studies of Framingham. Reprinted from Brindle et al. (45). CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; RR = relative risk; WOSCOPS = West of Scotland Coronary Prevention Study.

deprivation may be considered particularly important in certain regions, for example, where social gradients in health outcomes exist (10,19). Both Reynolds risk scores include C-reactive protein (CRP) (20,21). However, increasing the number of variables has advantages and disadvantages. For example, introducing a postal code-related measure of social deprivation will limit the use of the function in regions outside of this geographical region. One assumes that the more independent CVD risk factors are included, the better the risk estimate. However, the law of diminishing returns applies; once the basic risk factors are included, most of the predictive ability has been realized and the addition of extra factors results in only minor improvements (51), as will be discussed.

As more factors are included, the system becomes more complex, time consuming, and costly because a greater number of risk factors have to be measured to estimate the risk. This increase in complexity can impact the usage of the system. Some have suggested the use of additional factors to refine the risk estimate only in those at intermediate risk (52); this approach will be discussed in the following text.

Recently, there has been increasing interest in reducing the number of measurements (particularly laboratory measurements) required for risk estimation to increase ease of use and cost effectiveness. For example, the use of body mass index in place of lipid measurements has been shown to result in only minor reductions in discrimination of the function (8,53). The WHO/ISH risk charts are available in formats excluding lipid measurement (14); these are particularly suited to areas in the developing world where access to medical facilities is limited.

Although the performance and utilization of risk estimation systems are important, the bottom line is whether clinical outcomes improve with their introduction. The limited research into this area is addressed later in this review.

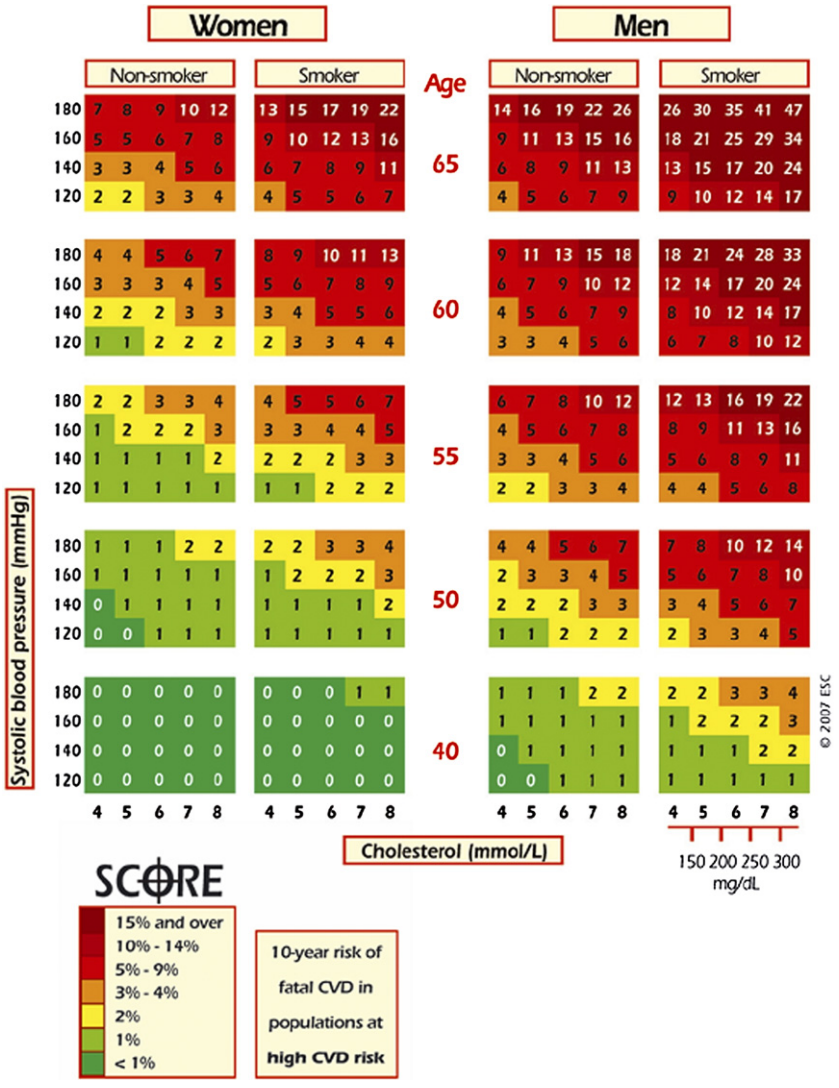


Figure 3 SCORE Chart for Use in High-Risk European Regions

CVD = cardiovascular disease; SCORE = Systematic COronary Risk Evaluation.

Universal Limitations of Risk Estimation Systems and Recent Advances in Overcoming These

One limitation of all risk estimation systems is that they assume constant effects of the risk factors at differing ages and levels of the other risk factors. The QRISK2 system has attempted to overcome the problem of differing effects of the risk factors with increasing age by including interaction variables between age and several of the other risk factors (11). However, this method still assumes that the interaction effect with age remains constant at all ages. Certain combinations of risk factors may act synergistically to increase risk in a manner that is more than additive. Cluster analysis and neural networks attempt to account for this, but introduce other problems, as discussed in the preceding text. The ideal situation would be to have an extremely large dataset (a whole country or even continent) in which there were numerous persons with each combination of risk factors and to examine the actual (not calculated) risk within each combination. In this way, particularly dangerous combinations of risk factors could be identified. However, development of such a dataset would be practically impossible, especially in the modern era when many of the identified risk factors already have been treated.

Recalibration of Risk Estimation Systems

As mentioned previously, risk functions developed in one region will tend to overestimate or underestimate risk in other populations with different baseline risks (45,54),

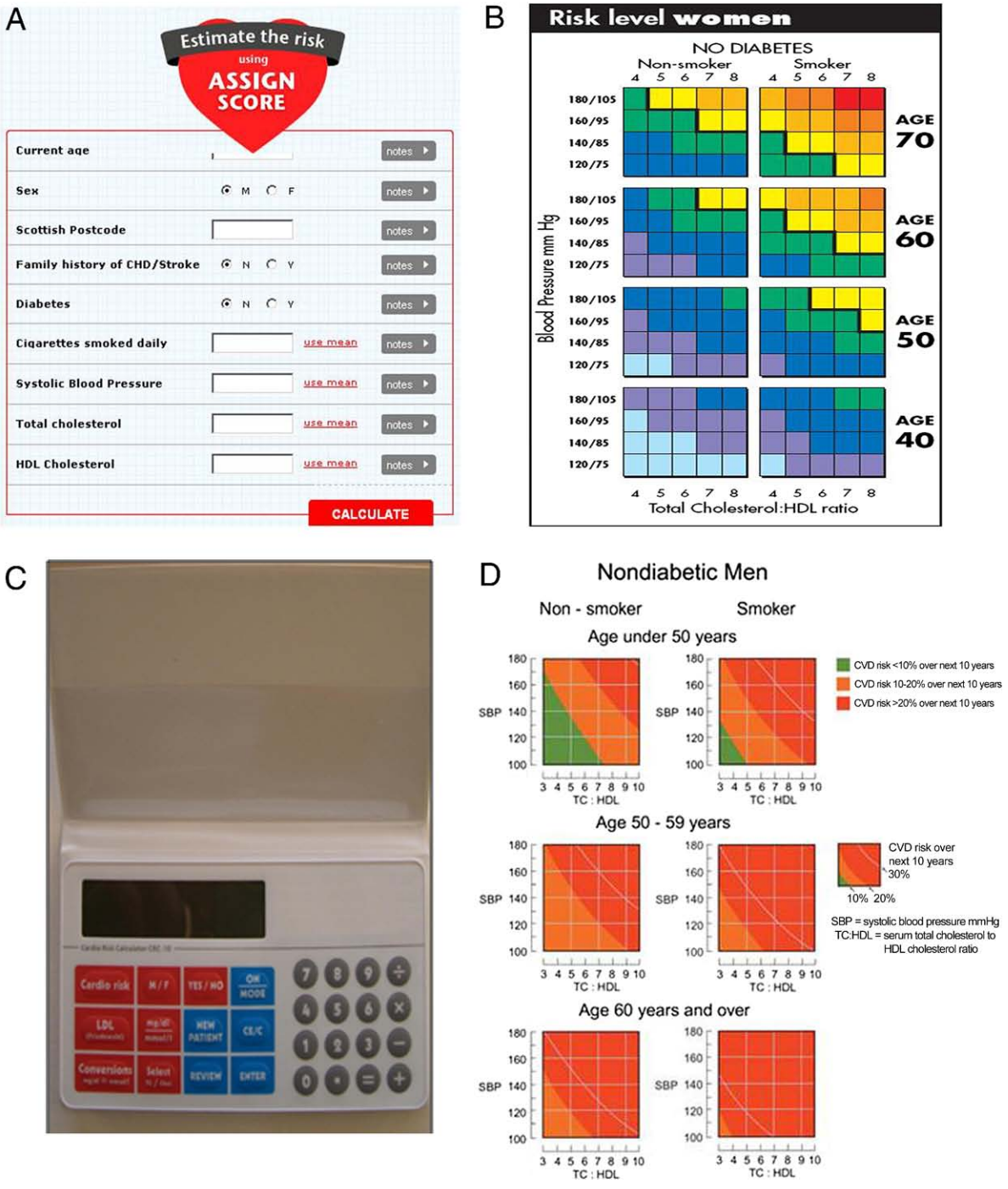


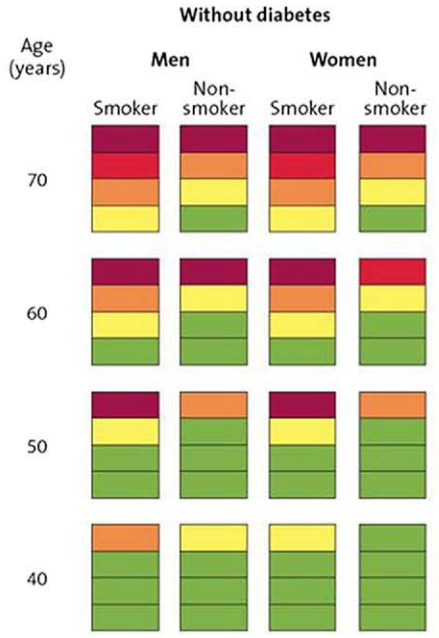
Figure 4 **Formats for Some Current Risk Estimation Systems**

(A) Interface for ASSIGN SCORE online calculator. **(B)** New Zealand risk chart (Framingham adaptation), reprinted with permission from the New Zealand Guidelines Group (18). **(C)** Portable Framingham risk calculator. **(D)** Joint British guidelines risk chart (Framingham adaptation), reprinted with permission from the British Cardiac Society et al. (48). *Continued on next page.*

because of either secular changes over time or regional differences. The ideal solution to this problem would be the continual generation of updated risk functions based on recent prospective cohort studies. While this is possible in some countries, for example, Finland (55) and Italy (56), this is not feasible in most areas. Recalibration of risk estimation systems represents a viable alternative.

Two recent, region-specific pieces of information are required: the current national CVD mortality rates (or CVD event rates) and representative surveys of risk factor levels in

E



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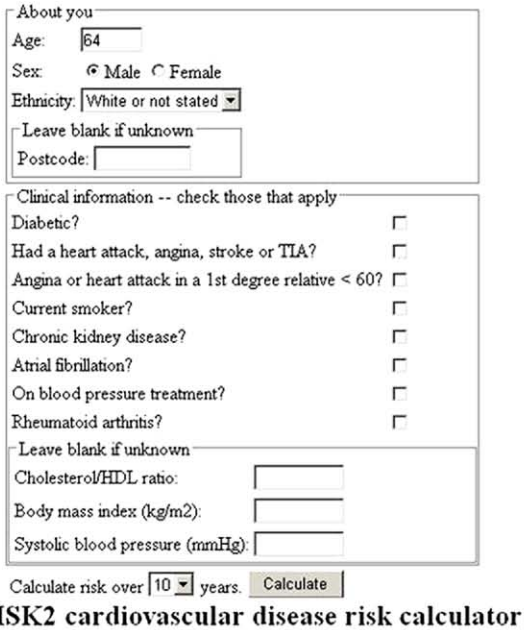

QRISK2 cardiovascular disease risk calculator

G

	10-year risk of a major coronary event in men				
Age (y)	0–4%	5–9%	10–19%	20–29%	≥ 30%
20–24	≤ 71				
25	< 66	= 67			
26	< 63	64–71			
27	< 60	61–69	= 70		
28	< 57	58–67	= 68		
29	< 55	56–64	= 65		
30	< 53	54–62	= 63		
31	< 51	52–60	61–62	= 63	
32	< 49	50–58	59–67	= 68	
33	< 47	48–56	57–65	= 66	
34	< 45	46–54	55–63	64–69	= 70
35	< 43	44–52	53–62	63–67	= 68
36	< 41	42–51	52–60	61–66	= 67
37	< 40	41–49	50–58	59–64	= 65
38	< 38	39–48	49–57	58–63	= 64
39	< 37	38–46	47–55	56–61	= 62
40	< 35	36–45	46–54	55–60	= 61
41	< 34	35–43	44–53	54–58	= 59
42	< 33	34–42	43–51	52–57	= 58
43	< 31	32–41	42–50	51–56	= 57
44	< 30	31–39	40–49	50–55	= 56
45	< 29	30–38	39–48	49–53	= 54
46	< 28	29–37	38–46	47–52	= 53
47	< 27	28–36	37–45	46–51	= 52
48	< 26	27–35	36–44	45–50	= 51
49	< 25	26–34	35–43	44–49	= 50
50	< 23	24–33	34–42	43–48	= 49
51	< 23	24–32	33–41	42–47	= 48
52	< 22	23–31	32–40	41–46	= 47
53	< 21	22–30	31–39	40–45	= 46
54	< 20	21–29	30–38	39–44	= 45
55	< 19	20–28	29–37	38–43	= 44
56	< 18	19–27	28–37	38–42	= 43
57	< 17	18–26	27–36	37–41	= 42
58	< 16	17–26	27–35	36–41	= 42
59	< 15	16–25	26–34	35–40	= 41
60	< 15	16–24	25–33	34–39	= 40
61	< 14	15–23	24–33	34–38	= 39
62	< 13	14–22	23–32	33–38	= 39
63	< 12	13–22	23–31	32–37	= 38
64	< 12	13–21	22–30	31–36	= 37
65	< 11	12–20	21–30	31–35	= 36
66	< 10	11–20	21–29	30–35	= 36
67	< 10	11–19	20–28	29–34	= 35
68	< 9	10–18	19–28	29–33	= 34
69	< 8	9–17	18–27	28–33	= 34
70	< 8	9–17	18–26	27–32	= 33
71	< 7	8–16	17–26	27–31	= 32
72	< 6	7–16	17–25	26–31	= 32
73	< 6	7–15	16–24	25–30	= 31
74	< 5	6–14	15–24	25–29	= 30
75	< 4	5–14	15–23	24–29	= 30

PROCAM Scoring Sheet

LDL* cholesterol (mg dL^{-1})		HDL† cholesterol (mg dL^{-1})		Systolic blood pressure (mmHg)		Smoking status	
≤ 100	0	≤ 35	11	< 110	0	No	0
101–105	1	36–37	10	110–119	1	Yes	12
106–110	2	38–39	9	120–129	2		
111–115	3	40–41	8	130–139	3	Family history	
116–120	4	42–43	7	140–149	4		
121–125	5	44–45	6	150–159	5	No	0
126–130	6	46–47	5	160–169	6	Yes	5
131–135	7	48–49	4	170–179	7		
136–140	8	50–51	3	≥ 180	8		
141–145	9	52–53	2				
146–150	10	54–55	1	Fasting blood glucose ≥ 120 mg dL^{-1} or diagnosis of diabetes mellitus			
151–155	11	> 55	0				
156–160	12						
161–165	13	Triglycerides (mg dL^{-1})					
166–170	14	< 100	0	No	0		
171–175	15	100–149	2	Yes (men)	9		
176–180	16	150–199	3	Yes (women)	11		
181–185	17	≥ 200	4				
186–190	18						
191–195	19						
≥ 196	20						

*Low-density lipoprotein, †high-density lipoprotein.

Figure 4 Continued

(E) Sample WHO/ISH risk chart. **(F)** Interface for QRISK2 online calculator. **(G)** PROCAM scoring sheet. CHD = coronary heart disease; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure; TC = total cholesterol; TIA = transient ischemic attack.

Table 4 Recalibrations of the Framingham and SCORE Risk Functions

	Recalibrated Versions
Framingham	China (58)
	U.S.—multiple ethnicities recalibration (57)
	Britain—including 8 different ethnicities (59)
	Asia (29)
	Mediterranean countries (60)
SCORE	Sweden
	Germany (61)
	Spain (62)
	Greece/Cyprus (63)
	Poland
	the Netherlands (27)
	Switzerland (64)

the population. The current survival is taken to equate to the baseline survival at the population mean level of risk factors. This new baseline is then adjusted to the individual person's level of risk factors, using the beta coefficients for each risk factor from the original risk function (57). This approach represents a feasible option in many countries where current mortality statistics are easily accessible and cross-sectional surveys of risk factor distributions have been conducted. The assumption here is that while the baseline survival changes from place to place and over time, the relative risks or beta coefficients associated with each risk factor remain the same.

Both the Framingham and the SCORE systems have been recalibrated for several different regions, as detailed in Table 4. The improvement in calibration is demonstrated for the Chinese recalibration of the Framingham function in Figure 5 (58). However, the discrimination of the function should remain virtually the same in the original and recalibrated versions of the risk function (58).

One advantage of the SCORE system is that the use of CVD mortality as the end point, as opposed to CVD events, facilitates the recalibration process (9), because reliable and recent CVD mortality statistics are readily available in many regions. This information is much less easily obtained and standardized when CVD event rates are required, and regional differences in coding represent a difficulty in systems that include less hard end points (15,16). This advantage strongly influenced the choice of CVD mortality as the end point in the SCORE project (9).

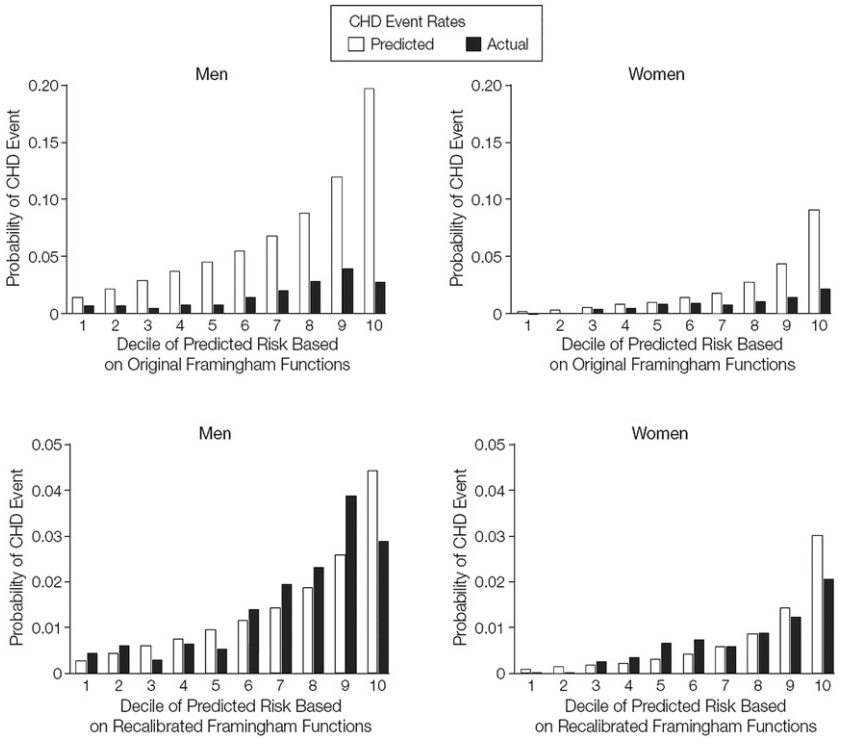

Figure 5 Improved Calibration of Framingham Function in Chinese Cohort After Recalibration

Calibration, predicted event rates **(open bars)** compared with actual coronary heart disease (CHD) event rates **(solid bars)**, based on **(A)** the original Framingham function and **(B)** the recalibrated Framingham function in the CMCS (Chinese Multi-Provincial Cohort Study). Reprinted from Liu et al. (58).

Table 5 Adjusted Odds Ratios for Risk Factors Newly Incorporated in Risk Function and Improvement in AUROC Afforded by Their Incorporation With Net Reclassification (Where Available)

Risk Factor	Study	Odds Ratio	End Point	Improvement in AUROC	Net Reclassification Index
Multiple biomarker score: BNP, CRP, homocysteine, renin, urinary albumin-to-creatinine ratio (66)	Framingham Offspring Study	1.84 (1.11–3.05) comparing the high quintile to the lowest 2 quintiles of multimarker score	Cardiovascular disease incidence: MI, coronary insufficiency, stroke, and heart failure	0.76–0.77	
HDL cholesterol (51)	Framingham	0.65 (0.53–0.80) for each 1 SD increase in HDL	Coronary heart disease incidence: MI, angina pectoris, coronary insufficiency, or CHD death	0.762–0.774	12.1%, $p < 0.001$
HDL cholesterol (67)	SCORE dataset	Women 0.60 (0.51–0.69); men 0.76 (0.70–0.83) per 0.5 mmol/l increase in HDL	Cardiovascular mortality	0.808–0.814	2.2%, $p = 0.006$
Heart rate (68)	The national FINRISK study	Men 1.19, women 1.20 per 10 beats/min increase in resting heart rate	Cardiovascular mortality	0.879–0.881	1.1%, $p =$ NS
hsCRP—women only (65)	Women's Health Study	hsCRP: 1.22 per 1-U increase in log (hsCRP)	CVD incidence: MI, ischemic stroke, coronary revascularization, and CVD deaths	0.813–0.815	5.7%, $p < 0.0001$
hsCRP (52)	Framingham Offspring Study	1.34 (1.14–1.58) for each 1-U increase in log (hsCRP)	MI and CHD death	0.863–0.865	11.8%, $p < 0.009$
Ethnicity and chronic diseases and interactions between age and several other risk factors (11)	QRISK2	Ethnicity: 8 ethnicities ranging from 1.97 (Pakistani women) to 0.51 (Chinese women) compared with white women Atrial fibrillation: 3.06 in men Renal disease: 1.70 in men	Cardiovascular disease incidence: CHD, stroke, TIA	Women 0.814–0.817, men 0.788–0.792, for all additions combined	
HbA1c	EPIC Norfolk		CHD incidence	Men 0.72–0.73, women 0.80–0.80	3.4% ($p = 0.06$ in men); 2.2% ($p = 0.27$ in women)

BNP = B-type natriuretic peptide; NS = not significant; TIA = transient ischemic attack; other abbreviations as in Table 3.

Assessing the Value of Incorporating New Risk Factors Into Risk Estimation Systems

Recently, much attention has focused on trying to improve risk estimation through the incorporation of new risk factors. Traditionally, the improvement in discrimination of risk estimation systems has been assessed by AUROC or Harrell's C statistic. There have been several demonstrations of the lack of improvement in discrimination, as measured by AUROC with the addition of these risk factors, despite the fact that many of these risk factors had strong and independent effects on the further occurrence of CVD (11,51,52,65,66). Table 5 shows some examples of the effect that inclusion of extra risk factors had on discrimination, as measured by AUROC.

However, AUROC was a technique developed for assessing the performance of a diagnostic test that has a straightforward yes/no answer, against that of a gold standard. A perfectly sensitive and specific test will result in an AUROC of 1. However, because risk estimation is just that, an estimate, a perfect AUROC will never be achieved. The highest AUROCs for risk estimation achieved to date have been in the region of 0.88, when tested on the same data from which they were derived (21). The usual AUROCs of risk estimation systems are in the region of 0.75 to 0.80. When one considers that age and sex alone can result in an AUROC of up to 0.70, clearly there is little room for improvement in AUROC with addition of risk factors beyond the conventional risk factors.

For this reason, there has been increasing interest in the development of more appropriate methods for assessing the improvement in performance afforded by incorporation of new risk factors (69). The method with most potential for clinical utility is reclassification.

Clinically, the most important feature of a risk estimation system lies in its ability to classify persons to appropriate risk categories, because treatment decisions are based on these classifications (43). Appropriate risk categories are those that are close to a threshold at which an intervention

recommendation is likely. Improvement of discrimination of a function in those at intermediate risk is particularly important (65).

A new method for assessing for superior classification has been developed by Pencina et al. (51). This measure, the net reclassification index (NRI), determines the net percentage of those who do and do not have an event over the observation time who are correctly reclassified using the new function. For example, in a person who develops the end point, upward movement to a higher risk category, when using the new risk function, would be considered correct reclassification (51).

This system has the advantage over previous reclassification measures of quantifying the reclassification in the net correct direction, as opposed to reporting the overall reclassification that occurs on addition of the new factor (51,65). Table 5 shows the NRIs associated with incorporation of various risk factors in risk estimation functions.

An interesting exploratory analysis by the Framingham group calculated the change in AUROC when risk factors were sequentially added to a model initially containing only age and sex (52). The risk factors were entered in the following order: systolic blood pressure, lipids, smoking, diabetes mellitus, and CRP. The increases in AUROC became sequentially smaller with each additional risk factor: 0.740, 0.767, 0.787, 0.795, and 0.799 for the listed risk factors, respectively. However, in spite of the relatively minor increases in AUROC, most of the additions were associated with improvements in reclassification, as measured by NRI: 10.8%, 7.0%, 7.7%, −0.5%, and 5.6% for each of the risk factors, respectively. The authors emphasize the fact that the value of incorporating risk factors is dependent on the order in which the risk factors were added to the model (52).

The exact utility of this system has yet to be determined. Some have suggested that those risk factors that provide superior classification could be measured in those at intermediate risk. High-sensitivity CRP has been suggested as a potential extra risk factor to measure in those at intermediate risk to further define risk in this group (52,65). It has been pointed out that the NRI depends strongly on the thresholds chosen for the risk categories (51). Therefore, it has been suggested that risk categories routinely used in clinical practice for decision making should be used in assessing reclassification (51).

Risk Estimation in Younger Persons

Younger persons will always be at low absolute risk (an obvious exception will be genetic defects that result in extreme levels of risk such as homozygous familial hypercholesterolemia), even when risk factor levels are very unfavorable. For example, looking at the 40-year age band of the SCORE chart in Figure 3 (9), no combination of risk factors will place a person in the high-risk category (≥5% 10-year risk of fatal CVD). Even a 40-year-old man who is severely hypertensive, severely hypercholesterolemic, and a smoker will still only have a risk of 4%. The same situation occurs with use of the Framingham function. For example, a study by Cavanaugh-Hussey et al. (70) points out that only the combination of current smoking and low high-density lipoprotein cholesterol could place a woman under the age of 65 years in the high-risk group based on the ATP (Adult Treatment Panel) guidelines (70). A similar situation was noted for men <45 years of age.

This represents a challenge when counseling these younger persons regarding the need for modification of lifestyle to reduce their risk (71). This is an important issue since modification of risk factors at this early stage affords the greatest opportunity for prevention of CVD. The earlier version of European guidelines recommended calculating what the person's risk would be at age 60 years if current risk factor levels were maintained (4). However, this was interpreted too literally by some, who suggested that this approach resulted in overmedication of the young (72). In the Fourth Joint Task Force guidelines, an alternative approach is provided: the relative risk chart (Fig. 6) (2).

This chart provides an estimate of the risk of a person with a certain combination of risk factors compared with a person of the same age and sex who has ideal risk factor levels. This relative risk may aid the physician in communicating to younger persons that although they are at low absolute risk, their risk is still "x" times higher than it could be if they had ideal risk factor levels. Taking the example of the 40-year-old hypertensive, hypercholesterolemic smoker, his low absolute risk of 4% equates to a relative risk of 12 times that of a man of his own age with ideal risk factor levels.

Other suggested methods for communicating regarding risk with younger persons include the calculation of lifetime risk, risk age, risk advancement periods, and expected survival. Lifetime risk is the risk of CVD developing in a person at some point during his or her lifetime (73). Using this method, the risk is highest for younger persons because they have a longer time available in which to develop the disease.

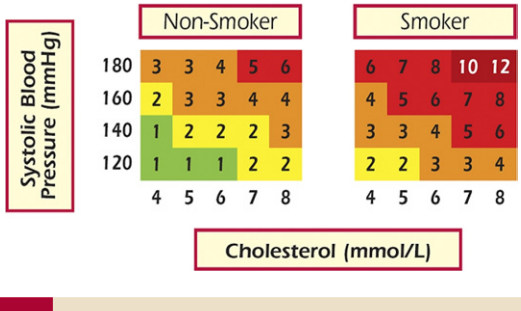

Figure 6 Relative Risk Chart

This chart may be useful in explaining to a younger person that, even if his or her absolute risk is low, it may still be 10 to 12 times higher than that of a person of a similar age with low risk factors.

Calculation of the individual person's risk age is another alternative that is easily understood (8,74). Using this system, the risk is expressed as extra life-years. Rate advancement periods can also be useful in communicating risk. This metric can be used when the risk of a disease (e.g., CVD) increases progressively with age. The rate advancement period is the average time period by which a certain rate (or risk for risk advancement period) of CVD is prematurely reached in subjects exposed to a risk factor or combination of risk factors (75). Another option that is presently being explored is the calculation of the expected survival (or life expectancy) associated with a combination of risk factors.

As pointed out by Hense (76), the risk chart format can be particularly useful for communication about risk. As well as showing absolute and relative risk, the chart can also be used by the physician to roughly calculate both risk age and risk advancement period (76). For example, the 40-year-old smoking, hypertensive, hypercholesterolemic man could be told that he has a "CVD risk age" of 65 years, since his 10-year CVD mortality risk is the same as that of a 65-year-old nonsmoking man with ideal risk factor levels, based on the SCORE chart (Fig. 3). The corresponding risk advancement period would be 25 years.

Risk Estimation in the Elderly

Current risk estimation systems vary in the age ranges to which they apply. Most can be used up to age 75 years (8,10–12). However, the SCORE function concentrates on the middle-aged group and is only recommended for use in the 40- to 65-year age range (9).

The use of risk estimation systems between the ages of 65 and 75 years is problematic because most of these systems were derived from cohorts of primarily middle-aged people, with older persons under-represented in the derivation cohorts. The same beta-coefficients for the risk factors were applied at all age ranges, meaning that the risks associated with risk factors in younger persons have been extrapolated to the older age groups. Substantial evidence points to the fact that although most conventional risk factors still function in the older age group, the relative importance of the risk factors changes with age (77), and therefore this use of the same beta-coefficients in all age groups may be inappropriate.

For example, in the INTERHEART study, hypertension, smoking, dyslipidemia, and diabetes remained significant risk factors for myocardial infarction in the >60 years age group but with significantly lower hazard ratios than for those in the <60 years age group (77). Conversely, in men >60 years of age, moderate alcohol consumption and physical activity became more important protective factors (77). (See Online Figure 1 for illustrations of these relationships.)

The accuracy of risk estimation has recently been shown to be substantially lower in older persons than in middle-aged persons (41,78,79). An analysis of the performance of the Framingham function in initially healthy 85-year-old subjects in the Leiden 85 Plus study showed very poor discrimination, with an AUROC of only 0.53, which was not significantly different from 0.50 (95% confidence interval: 0.43 to 0.64) (41). A function derived from the Leiden 85 Plus study and containing the same conventional risk factors resulted in a similarly low AUROC. In fact, of a number of risk factors and biomarkers, only homocysteine was a significant predictor of CVD mortality in this group. It should be remembered that age, which is the strongest contributor to the discrimination of virtually all risk functions, could not function in this cohort because all of the group's members were the same age at baseline. This contributes to the remarkably low AUROC. The dataset for this study was small: 302 participants with 35 events. Another study from the Netherlands of persons >70 years of age showed similarly poor discrimination, with AUROCs of 0.55 and 0.60 for the PROCAM and Framingham functions, respectively, for the prediction of CVD mortality (79).

Two recent studies have shown a significant improvement in discrimination of risk estimation systems in the elderly with the addition of a range of biomarkers including interleukin 6, CRP, troponin I, N-terminal pro–B-type natriuretic peptide, cystatin C, and carotid plaque burden. However, these improvements were based on internal validation and require confirmation in external studies.

An extension of the SCORE system is currently being developed. This system, SCORE O.P., will be derived entirely from a cohort >65 years of age at baseline. The system will utilize only the risk factors that remain significant predictors of CVD in the older age groups and will eliminate the problem of applying beta-coefficients derived from studies of younger persons to older persons. This alteration in derivation methods for the function may result in an improvement in risk estimation and may represent a more convenient approach to the measurement of multiple biomarkers in older people.

The second version of the QRISK function includes interactions between age and several other risk factors (11). The inclusion of these interactions allows for some of the difference in effect of risk factors at different ages. This inclusion may result in superior risk estimation in older age groups; however, this issue has not been examined to date.

Attempts to improve risk estimation in the older age group, however, will only solve one part of the problem of CVD prevention in the elderly. The other aspect that needs to be considered is what level to consider high risk (80). For example, using the SCORE function, all men >65 years of age will have a 10-year CVD risk >5%, and some have suggested that this can result in overmedication of older persons (80). The latest version of the European guidelines on CVD prevention recommends that a higher threshold of 10% may be considered high risk in older people (2).

Although recent randomized controlled trials of preventive measures in older and even very old persons have

demonstrated that significant benefits can be achieved (81), it is still uncertain whether risk stratification can assist in targeting these measures toward those who will benefit most, and if so, what threshold is appropriate in this age group. This issue requires further research.

Risk Estimation Systems and Outcomes

The vast majority of guidelines on CVD prevention now recommend that the intensity of preventive measures should be based on a person's total CVD risk (2,14,25). However, with the exception of the MRFIT (Multiple Risk Factor Intervention Trial) (82), which was undertaken at a time when risk factor treatments were of limited efficacy and against the background of falling CVD mortality rates, there has been no trial comparing the success of this approach with an ad-hoc, unifactor-based approach. The results of such a trial are not easy to predict. The unifactor approach might result in overtreatment of many persons with isolated risk factors and low total risk, and undertreatment of those who do not reach conventional risk factor thresholds for treatment of any one risk factor, yet are at extremely high total risk because of the combined effect of multiple factors.

Conversely, because the unifactor approach could result in treatment of a larger absolute number of people, it may result in a greater overall number of events avoided. However, the benefits of estimating total CVD risk and treating accordingly are 2-fold. The first is the direction of preventive efforts toward those who will be most likely to benefit. The second is the reassurance and avoidance of side effects in lower-risk persons who will, as a group, derive less benefit (83), which also has obvious economic implications. We suggest that if such an analysis were conducted, as well as calculating the benefits in both groups, adverse events in each group and costs should also receive due consideration.

While no specific evidence demonstrating the value of the high-risk approach is available, the logic of the approach is supported by the results of trials of pharmacotherapy for the prevention of CVD. Table 6, adapted from Jackson et al. (83), demonstrates the greater absolute risk reduction for stroke and CHD observed in randomized controlled trials of blood pressure and lipid-lowering treatment of those at higher baseline risk (due to pre-existing disease in this case) than lower-risk persons, despite an equivalent or even higher relative risk reduction. An interesting analysis by the same group calculated that the number needed to treat to prevent 1 CVD event in 5 years when using 3 preventive interventions (aspirin, lipid lowering, and blood pressure lowering) was only 6 in the very-high-risk group (30% 5-year risk of CHD) compared with 36 in the low-risk group (5% 5-year risk of CHD) (18).

The other question regarding risk estimation systems and their effects on outcome is whether the provision of risk estimation systems to health care professionals and/or the communication of information regarding total CV risk to patients results in benefit in terms of risk factor reduction. Of course, that will depend critically on the actual uptake of the system. Some smaller randomized controlled trials have addressed this issue (methodological details and results are described in Online Table 1) (49,74,84–87). Of note, there is substantial heterogeneity in both the designs and results of these studies. While most have shown a significantly greater reduction in risk factors in the intervention group, in general, the magnitude of the effect has been small. For example, CHAS (Cardiovascular Health Assessment Study) and the CHECK-UP (Cardiovascular Health Evaluation to Improve Compliance and Knowledge Among Uninformed Patients) study both showed greater improvements in cholesterol profiles and coronary risk scores in the intervention group. Four of the trials demonstrated greater reductions in blood pressure in subjects assigned to the risk estimation system intervention (49,74,84,86).

Particularly in the case of the study by Hanon et al. (87), the follow-up period may have been too short to detect a difference. For example, mortality benefits in the MRFIT trial among those randomized to the special intervention group only appeared after 10 years of follow-up (82). Because the majority of studies included patients already at substantial risk, in general, they failed to consider the reductions in treatment of low-risk persons. This underestimates the value of risk estimation as mentioned in the previous text.

Table 6 Absolute and Relative Risk Reductions Demonstrated in Meta-Analyses of Blood Pressure- and Lipid-Lowering Treatment in Higher- and Lower-Risk Groups

Lipid-Lowering Trials Meta-Analysis		
Baseline Risk of Trial Participants	**Absolute Risk Reduction (CHD)**	**Relative Risk Reduction (CHD)**
Few or no participants had a history of vascular disease	2.0% (1.7%–2.3%)	24% (17%–30%)
Most or all of participants had a history of vascular disease	3.4% (3.1%–3.6%)	24% (18%–21%)
Blood Pressure-Lowering Trials Meta-Analysis		
	Absolute Risk Reduction (Stroke)	**Relative Risk Reduction (Stroke)**
Few or no participants had a history of stroke	1.4% (1.2%–1.5%)	35% (29%–41%)
Most or all of participants had a history of stroke	4.4% (3.4%–5.4%)	24% (14%–34%)

Adapted from Jackson et al. (83).
CHD = coronary heart disease.

It is interesting to note that the studies that yielded the most promising results in terms of reduction in risk factors are the studies in which the patient was actually given the results of the risk profile (74,85). Additionally, both of these risk profiles included a presentation of the CV risk age, a measure that intuitively should be more comprehensible to the individual patient. This finding suggests that using risk estimation systems to emphasize to patients how elevations in their risk factors combine with each other to affect their risk of future disease improves both adherence to lifestyle advice and compliance with medication. Indeed, research has demonstrated that much of noncompliance with lipid-lowering medication is due to discontinuation by patients who fail to understand that their medication is still required.

Conclusions

In most people, atherosclerotic CVD is the product of more than 1 risk factor. A combination of several seemingly modest factors may result in a much higher total risk than a single, more impressively raised factor. Therefore, systems to help estimate total risk have been developed.

Most systems perform similarly in terms of discrimination (the ability to separate those who will develop an end point from those who will not). However, calibration (how closely predicted outcomes agree with actual outcomes) may vary widely if a risk estimation system is applied to a different population, or to a population that has seen a marked change in CVD mortality between the time when the function was derived and when it is applied. That can be dealt with by deriving a new system from a local and more contemporaneous cohort study. Often this will not be feasible, in which case recalibration is a practical alternative.

The addition of new risk factors often has a disappointingly small effect on overall performance, but can be useful in correctly reclassifying those at intermediate risk as above or below a chosen intervention threshold.

Young persons at low absolute but high relative risk of CVD need thought. Possibilities to illustrate their increased risk include relative risk charts and the calculation of lifetime risk, risk age, or risk advancement periods. The estimation of risk in the elderly remains a challenge.

While estimating total risk seems eminently logical, more research is required to quantify the clinical benefits—if any—and cost effectiveness of such an approach. But a greater problem is the underutilization of CVD prevention guidelines in clinical practice, and the real challenge is not to concern ourselves with competition as to which method of risk assessment is better but rather to encourage day-to-day risk evaluation and management.

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Key Words: cardiovascular disease ■ risk assessment ■ risk factors ■ recalibration.

APPENDIX

For Online Figure 1 and Table 1, please see the online version of this article.