Risk Prediction in Cardiovascular Medicine

Cardiovascular Risk-Estimation Systems in Primary Prevention
Do They Differ? Do They Make a Difference? Can We See the Future?

Marie Therese Cooney, MB; Alexandra Dudina, MB; Ralph D’Agostino, PhD; Ian M. Graham, MB

In this review of cardiovascular risk estimation, we focus on 4 key aspects: (1) The rationale for estimating cardiovascular risk; (2) a comparison of current cardiovascular disease (CVD) risk-estimation systems; (3) an examination of whether there is any evidence that cardiovascular risk estimation improves patient outcomes; and (4) how CVD risk estimation may change in the future. Some of the material presented is derived from a recent general review of cardiovascular risk scores that we have used to underpin the present, more focused discussion.

The Rationale for CVD Risk Estimation
The atherosclerosis underlying most CVD is rarely the result of a single risk factor, such as familial hyperlipidemia, but more usually the end result of the combined effect of several risk factors. If one considers single risk factors, even if the evidence for intervention is based on randomized controlled trials, either overtreatment or undertreatment may result. Consider, for example, Table 1, taken from the current Joint European Guidelines on the prevention of CVD in clinical practice. 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 level 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. To be clinically useful, a CVD risk-estimation system should be methodologically robust and easy to use, should address clinically relevant risk factors, and should result in a measurable health gain. These issues are addressed in the next section.

A Comparison of Current CVD Risk-Estimation Systems
Of the many risk-estimation systems in existence, the Framingham system is the best known both nationally and internationally and the most commonly used. The Framingham group must be acknowledged as pioneers in the field of risk estimation, having developed the first risk-estimation system and many of the statistical methods involved. The Framingham function has been modified for use in several different countries, and its use has been recommended by a variety of national and international guidelines for CVD prevention. Table 2 details the characteristics of the Framingham function and allows comparison with some other commonly used systems. Recently, several other systems have been introduced that offer advantages such as the inclusion of more recently described risk factors. In this review, we have concentrated mainly on those systems that are recommended by guidelines on CVD prevention.

A few key questions relevant to risk-estimation systems should be considered when the available systems are compared. These are tabulated for the different risk-estimation systems in Table 2 and discussed below.

Were the Appropriate Statistical Methods Used for Derivation of the Function?
The system should be derived from a study population with sufficient sample size that is representative of the population to which the function is to be applied. Framingham and ASSIGN risk scores are based on intermediate-sized samples that are representative of the general population. PROCAM (Prospective Cardiovascular Münster Study) is based on data from industrial employees and is, as such, less representative. SCORE (Systematic COronary Risk Evaluation) is considerably larger, being a pooled data set of 12 European cohort studies representing a total of 2.1 million person-years of observation; most of these cohorts were representative of the general population, although a small number of occupational cohorts were also included. This pooling of cohort studies means that more of the heterogeneity in baseline risk across Europe can be accommodated. QRSK has the advantage of being larger again, but the disadvantage is that because the data set has been assembled from a number of general practice (GP) registers, there is no standardization of methods, and missing data (as much as 70% for some variables) had to be imputed. An advantage of using

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ongoing GP registers is the possibility of continually updating the data.33 Two separate randomized controlled trials have been used as derivation data sets for the Reynolds risk scores for men and women.12,13

Several risk scores may be considered somewhat underpowered in women owing to lower event rates, particularly in PROCAM.10 An advantage of the Reynolds risk score is the larger number of women included.12 This may provide superior risk estimation in women, although this would need to be tested in an external validation study.

The outcome predicted by the system should be clearly defined so that it can be standardized easily, and it should be relevant to the outcomes shown to be affected by preventive measures in randomized controlled trials. Early systems usually estimated coronary heart disease risk.15 Earlier versions of the Framingham risk score included “softer” end points, for example, onset of exertional angina. This may cause difficulty with standardization. The end point of total CVD events in the most recent version of the Framingham risk score includes outcomes such as intermittent claudication and transient ischemic attack but provides the option of estimating risk of only hard CVD events.6

The goal of primary prevention should be the avoidance of all vascular disease, including stroke and peripheral vascular disease in addition to coronary disease. Because all atherosclerotic diseases of the vascular tree share the same risk factors, it is generally considered that the most appropriate outcome for risk-estimation systems is total CVD.6,7 It is useful, however, to retain the ability to estimate the 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.34 SCORE estimates risk of CVD mortality as opposed to combined fatal and nonfatal events.7 This end point, although less intuitively popular, has the advantage that it is easily standardized across different countries and cohort studies and facilitates the recalibration process, as discussed below.

Several statistical methods can be used for the derivation of these risk-estimation functions. The most commonly used is the proportional hazards model, either Cox (semiparametric) or Weibull (parametric). Both are preferred to logistic regression because they can account more appropriately for variable follow-up times and losses to follow-up. In the SCORE function, age was used as part of the time variable; this allowed the effect of age to vary at different ages.7

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

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age, y</th>
<th>Cholesterol, mmol/L (mg/dL)</th>
<th>SBP, mm Hg</th>
<th>Current Smoker</th>
<th>SCORE Risk, %</th>
<th>10-Year Risk of Fatal CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>60</td>
<td>8 (309)</td>
<td>120</td>
<td>No</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>60</td>
<td>7 (271)</td>
<td>140</td>
<td>Yes</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>60</td>
<td>6 (232)</td>
<td>160</td>
<td>No</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>60</td>
<td>5 (193)</td>
<td>180</td>
<td>Yes</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

F indicates female; M, male.

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The World Health Organization/International Society of Hypertension risk-prediction charts offer an advantage in that they have been developed for each specific World Health Organization subregion.11 The methods, however, are problematic.11 From the limited description provided, it appears that charts were developed by creating a hypothetical data set for each region based on the risk factor prevalence in that area according to the Collaborative Risk Assessment Project.35 The β-coefficients for the risk factors were based on previous prospective studies. The relative risk for each individual was then scaled according to the baseline risk in that region, as estimated from the Global Burden of Disease Study, to estimate the absolute risk. As has been acknowledged by the authors, these methods require substantial further investigation to determine their accuracy and validity.11

The Reynolds risk scores offer the advantage of including family history and C-reactive protein in the calculation of total CVD risk.12,13 The improvement in performance afforded by the inclusion of these extra risk factors will be discussed below.

### How Does the Function Perform on Internal and External Validation?

Performance is assessed in terms of discrimination, or the ability of the function to separate those who will develop the end point from those who will not, and calibration, a measure of how closely the predicted outcomes agree with the actual outcomes.

**Discrimination** is often measured with an area under the receiver operating characteristic curve (AUROC), which is a means for expressing the maximum achievable sensitivity and specificity. An AUROC of 1 indicates perfect discrimination, and 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. The Harrell C statistic gives the same information but can be used with variable follow-up.

**Internal validation** is the assessment of the performance of the risk function in the data from which it was derived. As shown in Table 2, risk-estimation systems generally perform well when assessed in this way.5–10 Although important for checking the mathematical performance of the model used and appropriate fit, this type of analysis should not be used for the comparison of new functions with existing functions, because there will be a bias toward the new function that was derived specifically from the test data set. It is more appropriate to compare the performance of functions in an external data set, and caution is required in the interpretation of reports of superiority of new functions that have been examined in this way.8,9

Both Framingham14,15 and SCORE7 have been assessed in a number of external validation studies and have shown good discrimination, as shown in Table 2.23–29 In general, discrimination is superior in women and inferior in the elderly.36 Some studies have shown reduced discrimination with the Framingham function.25,36 Explanations for this include differences between the end point predicted by the function and the end point in the observational study23,25,37 and the examination of individuals within a narrow age range.36 QRISK demonstrated good discrimination when externally validated
in the United Kingdom’s THIN (The Health Improvement Network) GP register.27 Information on external validation of other risk functions, including PROCAM,10 World Health Organization/International Society of Hypertension, and ASSIGN, is limited.

In addition to these measures of summary discrimination, the threshold discrimination is also important, particularly in clinical practice. The sensitivity and specificity of these risk functions at different cut points for low and high risk should also be reported.38

**Calibration** is measured in terms of either goodness of fit, with lower values indicating better fit and values <20 generally considered good fit, or predicted-to-observed ratios, with values closer to 1 indicating better fit. Values >1 indicate overestimation and values <1 indicate underestimation.

### Table 2. Characteristics of Current Risk Estimation Systems (WHO/ISH, SHHEC)

<table>
<thead>
<tr>
<th></th>
<th>Framingham6</th>
<th>SCORE7</th>
<th>ASSIGN–SCORE8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data</strong></td>
<td>Prospective studies: Framingham Heart Study and Framingham offspring study. Latest version includes both</td>
<td>Pooled prospective studies</td>
<td>SHHEC Prospective study</td>
</tr>
<tr>
<td><strong>Sample type</strong></td>
<td>Volunteer</td>
<td>Mostly random samples from general population, some occupational cohorts</td>
<td>Random</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>3969 Men and 4522 women</td>
<td>117 098 Men and 88 080 women</td>
<td>6540 Men and 6757 women</td>
</tr>
<tr>
<td><strong>Statistical methods</strong></td>
<td>Cox (Weibull; earlier versions14)</td>
<td>Cox and Weibull</td>
<td>Cox</td>
</tr>
<tr>
<td><strong>Calculates</strong></td>
<td>10-Year risk of CHD events originally. Latest version: 10-year risk of CVD events. NCEP ATP III version: 10-year risk of hard coronary events</td>
<td>10-Year risk of CVD mortality</td>
<td>10-Year risk of CVD events</td>
</tr>
<tr>
<td><strong>Age range, y</strong></td>
<td>30–75</td>
<td>40–65</td>
<td>30–74</td>
</tr>
<tr>
<td><strong>Variables</strong></td>
<td>Gender, age, total cholesterol, HDL cholesterol, SBP, smoking status, diabetes, hypertensive treatment</td>
<td>Gender, age, total cholesterol or total cholesterol/HDL cholesterol ratio, SBP, smoking status. Versions for use in high- and low-risk countries</td>
<td>Gender, age, total cholesterol, HDL cholesterol, SBP, smoking (no. of cigarettes), diabetes, area-based index of deprivation, family history</td>
</tr>
<tr>
<td><strong>Formats</strong></td>
<td>Simplified scoring sheets. Color charts have been generated for some guidelines, eg, JBS and New Zealand guidelines. Online calculators. Portable calculators</td>
<td>Color-coded charts, HeartScore: online and CD-based stand-alone electronic versions</td>
<td>Online calculator</td>
</tr>
<tr>
<td><strong>Developments</strong></td>
<td>Latest version includes version based on nonlaboratory values only, substituting BMI for lipid measurements</td>
<td>National, updated recalibrations</td>
<td></td>
</tr>
<tr>
<td><strong>Recommended by guidelines</strong></td>
<td>NCEP guidelines,20 CCS guidelines.5 Other national guidelines recommend adapted versions, including New Zealand27</td>
<td>European guidelines on CVD prevention2</td>
<td>Recommended by SIGN21</td>
</tr>
<tr>
<td><strong>Internal validation: discrimination</strong></td>
<td>AUROC: Men 0.76 (0.75–0.78), women 0.79 (0.77–0.81)</td>
<td>AUROC high risk 0.80 (0.80–0.82), AUROC low risk 0.75 (0.73–0.77)</td>
<td>AUROC: Men 0.73, women 0.77</td>
</tr>
<tr>
<td><strong>Internal validation: calibration</strong></td>
<td>HL: Men 13.48, women 7.79</td>
<td>Not specified</td>
<td>Observed 10-year CVD incidence rates: Men 11.7%, women 6.4%. Median ASSIGN score: Men 11.7%, women 6.2%</td>
</tr>
<tr>
<td><strong>External validation: discrimination</strong></td>
<td>PRIME Study22: Belfast 0.68, France 0.66, Dutch study23: 0.86 (0.84–0.88), Cleveland Study24: 0.57, China25: Men 0.75 (0.72–0.78), women 0.79 (0.74–0.85), THIN (UK)27: Men 0.74 (0.73–0.74), women 0.76 (0.76–0.76), EPIC Norfolk28: 0.71, UK Women (BeHIS29): 0.66 (0.62–0.69)</td>
<td>Dutch study24: 0.85 (0.83–0.87), Cleveland Study24: 0.73, Norwegian Study25: Range for different age groups, men 0.65–0.68, women 0.66–0.72, Austrian Study27: Men 0.76 (0.74–0.79), women 0.78 (0.74–0.82), Icelandic Study27: 0.80 (0.78–0.82), SCORE high 0.80 (0.77–0.82), SCORE low Not assessed</td>
<td></td>
</tr>
</tbody>
</table>

**WHO** indicates World Health Organization; ISH, International Society of Hypertension; SHHEC, Scottish Heart Health Extended Cohort; QRISK1 and QRISK2, versions 1 and 2 of the QRISK CVD risk algorithm; PROCAM, Prospective Cardiovascular Münster Study; CHD, coronary heart disease; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; SBP, systolic blood pressure; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction; HbA1C, hemoglobin A1C; JBS, Joint British Societies; CD, compact disc; CCS, Canadian Cardiovascular Society.
Figure 1 illustrates the strong secular trends in coronary heart disease rates that have been occurring over the last 50 years, as well as the marked regional differences in the baseline risk of coronary heart disease. Owing to these differences in baseline risk, the calibration of risk functions will change over time, as well as when a function derived from 1 population is applied to a population with a different baseline risk of CVD. This was demonstrated in a systematic review by Brindle and colleagues; for example, they showed that the Framingham function tended to overestimate risk when applied to some European populations. Risk functions that were well calibrated to the population at the time they were derived will tend to overestimate risk, because the incidence of disease decreases with time. Recalibration of risk functions, which will be discussed below, provides a feasible means for overcoming this problem.
The net reclassification index is a measure of the net percentage of those who do and do not develop the end point within the time period who are correctly reclassified to a different risk category when a new risk factor is added to the risk-estimation system. This will be discussed below.

In What Format Is the System Presented, and Do These Formats Promote Ease of Use?
Clearly, risk-estimation systems need to be based on statistically sound methods and should accurately estimate risk in the population to which they are to be applied. However, the format of the system is equally important, because the extent to which they are actually used in clinical practice may depend on the user-friendliness of the system. In general, clinicians prefer simpler formats.41,42 The Framingham scoring sheets that were developed for the National Cholesterol Education Program’s Adult Treatment Panel III guidelines are well known and widely used in North America.43 The colored SCORE charts7 are a good example of a simple format. As shown in Figure 2, the chart also incorporates the integer value for the 10-year risk, which results in improved accuracy compared with charts that use colored risk bands only. This format was based on that used in the risk charts in the New Zealand guidelines on hypertension.17

Electronic interactive systems offer a substantial advantage in that as many risk factors as required can be incorporated. The disadvantage to this is the increase in complexity of the system, which may have an impact on usage in clinical practice.44 An approach that has been adopted successfully in New Zealand, called PREDICT-CVD, is the integration of the electronic risk-estimation system into the GP database so that the estimate is calculated automatically for each patient.45

What Variables or Risk Factors Are Included in the Function, and Are These Appropriate?
Most risk-estimation systems include age, gender, 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 determinants and prevalent in the population to which system is to be applied (eg, 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 on the basis of whether they improve risk estimation, because those individuals identified as high risk can still modify their risk by favorably altering their other risk factors. Systems that use only easily measured nonlaboratory measures have been developed recently, as discussed below.

Do Risk-Estimation Systems Make a Difference?
This critical question is not easy to answer completely on the basis of the available evidence. The question can be interpreted in a number of ways:

- Is the high-risk approach to CVD prevention, wherein high-risk individuals are identified and selected for more intensive preventive measures on the basis of the combined effect of multiple risk factors, superior to a single risk factor approach in which each risk factor above a certain threshold is treated to target, irrespective of total CVD risk?
- Does provision of a risk-estimation system result in benefit in terms of risk factor reduction? Arising from this, does communication with the individual patient about their total CVD risk provide further benefit?

The first is the central question but has the least evidence available to answer it. Although virtually all guidelines on CVD prevention stress the importance of a total CVD risk–based approach,2,5,11,17,21,22 there has been no recent randomized controlled trial assessing the benefit of the total CVD risk approach to an ad hoc single risk factor approach. One exception was the Multiple Risk Factor Intervention Trial (MRFIT); however, this was conducted during a period when
baseline CVD rates were already falling and when the effectiveness of preventive measures for the reduction of risk was modest.46

The results of such a trial are difficult to predict, but were it to be conducted, it should focus on cost-effectiveness and the avoidance of medication-related side effects, as well as on the absolute reduction in events in each group. This is because the high-risk approach is concerned not only with treating those who will benefit the most but also with avoiding unnecessary cost and adverse effects in a large number of individuals of whom only a modest number will derive any benefit.

The rationale behind the high-risk strategy is supported by the results of randomized controlled trials of preventive measures that have shown that treatment of higher-risk individuals results in substantially greater reductions in absolute risk, even though relative risk reductions may be very similar in individuals with higher and lower total risk.22 Table 3 shows how the number needed to treat for 1, 2, or 3 preventive interventions increases sharply as the absolute risk of the group declines.

The fact that the high-risk approach targets the individuals at highest risk for intensive risk factor modification should not be interpreted as suggesting that risk factor modification is not efficacious in low-risk individuals. Indeed, statin therapy has been demonstrated in randomized controlled trials of populations free to overt disease, to be highly effective in terms of relative risk reduction.47,48 The population approach (ie, favorably shifting the risk factor distribution of the entire population) is an equally important component of an effective preventive strategy. We have explored this issue in a recent review and modeling exercise.49

Table 3. Estimated Number Needed to Treat for 1, 2, and 3 Interventions Based on Level of Absolute 5-Year Risk of CVD Events

<table>
<thead>
<tr>
<th>Risk Level:</th>
<th>No. Needed to Treat for 5 Years to Prevent 1 Event*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD Risk, %</td>
<td>1 Intervention (25% Risk Reduction)</td>
</tr>
<tr>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
</tr>
</tbody>
</table>

*Based on the conservative estimate that each intervention (aspirin, blood pressure treatment [lowering systolic blood pressure by 10 mm Hg], or lipid modification [lowering low-density lipoprotein cholesterol by 20%]) reduces cardiovascular risk by ~25% over 5 years.
consider that population-wide risk factor reductions should be achieved through lifestyle changes, although the “polypill” approach of providing low-dose generic pharmacotherapy has also been advocated.50 Further discussion of this issue is beyond the scope of the present review.

In answering the second question, there are some randomized controlled trials of the use of risk-estimation systems and effects on risk factor control available.44,51–54 These trials are noteworthy for considerable heterogeneity of methodology, both in terms of the intervention provided and the end point assessed. The majority have shown greater reductions in risk factor levels in those randomized to intervention.44,53,54 which was either provision of a risk-estimation system (for the healthcare provider to use) or a summary of the patient’s total CVD risk displayed in the chart, although the results have not been entirely consistent.51,55

The majority of these trials have not been able to account for the reduction in unnecessary prescription of medications to lower-risk individuals because they have included only higher-risk individuals.44,51,53,55 However, the study by Hall et al51 showed that within the intervention group, there was an increase in prescription of preventive medications to high-risk individuals without a change in the low-risk group.

Some of the trials may not have had a long enough time period to show the full effects, especially given that the mortality benefits in the MRFIT special intervention group only became evident after 10 years of observation.56 The follow-up periods in these studies ranges from only 8 weeks55 to a maximum of 18 months.54 Interestingly, the 2 trials that demonstrated the most impressive increase in risk factor control in those assigned to intervention both provided the individual patient with a printout of their results, and both of these included an easily understood measure of total CVD risk: Heart age or CVD risk age.53

The integration of a risk-estimation system with GP medical record databases may help to solve the problem of underusage of risk-estimation systems in clinical practice. This would be feasible in countries in which computerized medical records systems are available. Certainly, this approach has been very successful in New Zealand, where a 4-fold increase in recording of total CVD risk in medical notes was demonstrated after the introduction of the PREDICT-CVD system.45

Risk-Estimation Functions: Can We See the Future?

A universal 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 use of interaction variables between age and some of the other risk factors, as in QRISK24 and the National Cholesterol Education Program Adult Treatment Panel III version of Framingham,13 may help to improve this situation. Techniques including cluster analysis and neural networks can be useful in allowing for the additive effects of different risk factor combinations, but as mentioned above, these complicated systems are difficult to apply in clinical practice. It would be ideal to examine the actual risk associated with each combination of risk factors in an extremely large data set (a whole country or even a continent), but such a large data set is very unlikely to ever be assembled and would be nearly impossible to achieve in modern times, especially because the majority of people in the higher-risk categories would already be undergoing treatment.

Recalibration of Risk-Estimation Systems

As mentioned above, risk functions developed in 1 region will tend to overestimate or underestimate risk in other populations with different baseline risks,50,57 either owing to secular changes over time or to regional differences. Although some countries have up-to-date, local cohort data available for the generation of country-specific risk functions,58,59 many do not. In this situation, the recalibration process is a feasible alternative.

The process uses national CVD mortality (or CVD incidence) figures and recent estimates of local risk factor distributions to create a new baseline of CVD risk that is recent and country-specific. The β-coefficients for the risk factors from the original risk function are then used to adjust the baseline to the individual’s risk factor levels.60 The assumption here is that the relative risks associated with the risk factors do not change over time or from place to place.

The Framingham function has been recalibrated for a number of regions in Europe61,62 and Asia26,63 and for different ethnicities within the United States.60 SCORE has been recalibrated for several European countries.24,64–67 Both country-specific paper risk charts and versions of HeartScore have been developed and are available on the Internet.68 We have previously alluded to the fact that the use of CVD mortality as the end point in SCORE facilitates the recalibration process,5 because reliable and recent CVD mortality statistics are readily available in many regions and can be more precisely standardized across different countries.

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

The limitation of the AUROC for assessing the additional benefit to risk estimation of the incorporation of new risk factors has been increasingly realized recently. Several risk factors that are known to have important and independent effects on CVD outcomes have resulted in little or no improvement in discrimination (in terms of AUROC) when added to risk-estimation systems. These include high-density lipoprotein (HDL) cholesterol,69,74 multiple biomarkers,71 high-sensitivity C-reactive protein,70,72 hemoglobin A1C,28 and the combination of ethnicity, chronic diseases, and age interactions.9 Moreover, this lack of improvement in AUROC also occurs for conventional risk factors. For example, the Framingham investigators demonstrated that the addition of lipids (both HDL and low-density lipoprotein cholesterol) to a function that already contained gender, age, and systolic blood pressure resulted in a minor improvement in AUROC, from 0.740 to 0.767.70 AUROC was developed initially to compare the performance of diagnostic tests, which have a “yes/no” result, with “gold standards.” Therefore, AUROC analysis may not be entirely appropriate for assessment of the accuracy of systems that give an estimate of risk, not a yes/no answer relative to the future development of disease. This, combined with the fact that age and gender alone can provide high AUROCs (up to 0.75), is probably responsible for the lack of improvement when additional risk factors are added.
Recently, the concept of reclassification has received more attention. The ability of a system to correctly classify individuals into risk categories is particularly important because treatment decisions are based on these categorizations. The Framingham group has recently developed a new statistic that is particularly useful for assessing the added value of incorporating new risk factors into risk-estimation functions: The net reclassification index. It is a measure of the net percentage of individuals who are correctly reclassified to a more appropriate risk category on the basis of the new function, and it is calculated separately in those who do and do not develop the end point within the specified time. For example, if the new risk function reclassifies an individual who did develop the end point to a higher-risk category, this is considered a correct reclassification and vice versa.

With the net reclassification index, the addition of the following risk factors has been shown to result in superior risk estimation in terms of risk classification: HDL cholesterol, high-sensitivity C-reactive protein, and hemoglobin A1C. This suggests the question of whether these extra risk factors should be used only in those at intermediate or borderline risk, because these are the individuals in whom inclusion will result in a clinically relevant change in the risk estimate. This would afford the advantage of improving risk estimation in individuals who will benefit while avoiding unnecessary further laboratory testing in others.

Simple Risk-Estimation Systems
Because of the increasing emphasis on cost-effectiveness, there have been a number of simplified risk-estimation systems developed recently that use a reduced number of risk factors. These systems also enhance accessibility, because several eliminate the need for laboratory measurements. This means that the risk estimate can be calculated on the basis of risk factors that can all be obtained in the GP’s office. Two groups have shown that the use of body mass index in place of lipid measurements results in only very slightly inferior performance. The World Health Organization/International Society of Hypertension have developed their risk charts in formats that exclude lipid measurements; these are particularly suited to areas in the developing world where access to medical facilities is limited.

Systems for Estimating Risk in Younger Individuals
As can be seen from the SCORE chart in Figure 2, age is the most important factor in determining the absolute risk of CVD. For this reason, all younger individuals will be at low absolute risk, irrespective of their risk factor levels (an obvious exception will be those with genetic defects that result in extreme levels of risk, such as homozygous familial hypercholesterolemia). This may cause difficulty when communicating to these younger individuals the need for lifestyle change to modify their risk. This has been noted when using the Framingham function also. Previously, European guidelines suggested extrapolating the risk to age 60 years to show younger individuals that although their risk was currently low, without modification it would place them at high risk by the time they were 60 years old. However, this was interpreted too literally by some, who suggested this approach resulted in overmedication of young individuals. The approach recommended in the fourth version of the European guidelines is the relative risk chart. This chart, shown in Figure 3, can be used to show younger individuals that although their risk is currently low, it may still be up to 12 times higher than the risk of an individual of their same age and gender who has ideal risk factor levels.

Heart age or CVD risk age, a concept introduced by the Framingham group, is becoming increasingly popular for communicating risk to younger individuals. It expresses the risk as life-years lost or gained for the individual’s actual age. Other approaches that are useful include calculation of lifetime risk and risk advancement periods. Risk advancement periods express the risk associated with a risk factor or combination of risk factors as the age span in years equivalent to the same level of risk. As highlighted by Hense, the risk chart is a useful tool in communicating these measures to patients.

Risk Estimation in the Elderly
Most of the current risk-estimation systems can be used up to age 75 years; however, the age range for SCORE is more limited, focusing on the middle-aged group from 40 to 65 years. Risk factors are known to function in the older age group; however, it is well recognized that the relative risks may differ from those of younger individuals. Additionally, some risk factors may become more important; for example, physical activity and moderate alcohol intake were stronger protective factors in older men than in younger men in the INTERHEART study.

In general, current risk-estimation systems use the same β-coefficients in each age group. These β-coefficients have been derived mainly from data based on younger individuals, and this extrapolation to older age groups may be inappropriate. This could have contributed to the inaccuracy of risk estimation in this age group that has been demonstrated in many studies. However, QRISK2 and the National Cholesterol Education Program Adult Treatment Panel III version of the Framingham risk score have incorporated interactions between age and other risk factors.

It has been demonstrated recently that the addition of other risk factors, including biomarkers and markers of subclinical disease, can improve risk estimation in this age group. Another approach to improvement of risk estimation in older individuals is the generation of a risk function derived specifically from data from older individuals. The SCORE
group plans to investigate the benefit of this change in methods in a project known as SCORE OP. This may provide a more convenient approach to improving risk estimation than the measurement of multiple extra risk markers.

Recent randomized controlled trials and meta-analyses of preventive measures, including lipid lowering and pharmacotherapy for hypertension, have suggested benefits in older\textsuperscript{43,85} and even very old\textsuperscript{86} individuals. Therefore, prevention of CVD should be considered possible in the elderly. This makes the requirement for accurate risk estimation more obvious. However, the optimal threshold for defining high risk in this age group needs some investigation. Whether the approach of targeting those with the highest total CVD risk is still appropriate with advancing years also requires consideration.\textsuperscript{87}

Conclusions

The rationale for developing and using a risk-estimation system lies in the fact that in most people, atherosclerotic CVD is the product of $>1$ 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.

With regard to comparative performance, 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 the predicted outcomes agree with actual outcomes) may vary widely if a risk-estimation system is applied to a different population or to one that has seen a marked change in CVD mortality between the time when the function was derived and when it was applied. This 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 being above or below a chosen intervention threshold.

Does the Use of a Risk-Estimation System Improve Outcomes?

Although it is established that high-risk individuals gain the most from risk factor control, the answer is at most a qualified “yes,” because this issue has been researched insufficiently. In general, a systematic approach to total risk estimation appears to result in better risk factor control, but there are insufficient randomized controlled trial data to establish better outcomes in terms of clinical end points. The use of risk-estimation systems to avoid excessive use of medications in low-risk individuals also deserves study.

The Future

Risk-estimation systems can only help if they are applied; dissemination and implementation strategies are being reviewed in many countries. Survey data\textsuperscript{42} support the provision of simpler systems of risk estimation and management, and these are now emerging. Some of these do not require laboratory tests. Electronic risk estimation, preferably automated and linked to the patient’s electronic record, is evolving.

The assessment of risk in the young and old poses different challenges. In young people, a low absolute risk may conceal a high relative risk. Possibilities to illustrate their increased risk include the use of 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. The extrapolation of current thresholds for intervention to older persons could result in overmedication. Furthermore, risk factor effects are not constant as a person ages, and new risk systems will need to accommodate this.

The addition of newer biomarkers has had a very modest effect on the overall performance of current risk-estimation systems but may be more useful in reclassification of those at intermediate risk. Recalibration can markedly improve the performance of systems when applied to different populations.

Although estimating total risk seems eminently logical, more research is required to quantify the clinical benefits, if any, and cost-effectiveness of such an approach. 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 the implementation of day-to-day risk evaluation and management.

Disclosures

None.

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