Review of tools of cardiovascular disease risk stratification: interpretation, customisation and application in clinical practice

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ABSTRACT

Cardiovascular Disease (CVD) is the leading cause of death in both developed and developing countries. While it is relatively easy to identify those who are obviously at high risk and those at the lowest risk for CVD, it is often the large group of individuals with what appears to be modestly abnormal risk factors who contributes most to the burden of CVD. This is where estimation of CVD risk is necessary. Many tools for risk assessment have been devised. All these risk scores have their own inherent advantages and disadvantages. Furthermore, they may also not be directly applicable to a local population. Ideally, each country should have its own risk score that takes into account other factors as well. In the interim, it is worthwhile to be familiar with one of these scores, select one that is most appropriate for your patient and discuss treatment options based on the estimated risk.

Keywords: cardiovascular disease, global cardiovascular risk, risk assessment, risk score charts

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INTRODUCTION

Cardiovascular Disease (CVD) still remains the leading cause of morbidity and mortality in developed and most developing countries.[1,2] CVD encompasses many clinical conditions, but all of them are caused by a common underlying pathophysiology of accelerated atherosclerosis. Many diseases cause accelerated atherosclerosis, the main culprits being diabetes mellitus, hypertension and dyslipidaemia. While each individual CVD risk factor, especially when it is the only abnormally high-risk factor in an individual, can result in CV events like myocardial infarction or stroke, it is usually a combination of modestly elevated risk factors that impose the greatest risk to the individual. It is now known that patients often have more than just one CV risk factor. Moreover, the presence of several CV risk factors together is not only a simple additive effect but a multiplicative effect, as shown in many studies.[3]

It is therefore a necessity to take into account the overall CVD risk of an individual in order to determine whether each or all of the modestly elevated risk factors need to be actively managed with non-pharmacological and even more likely, with pharmacological therapy. This is extremely important because we need to identify those who will benefit most from intervention, especially in the light of limited resources, where we aim to save the greatest number of lives at the lowest cost. We also need to balance our pharmacological intervention with adverse events of drugs, i.e. weigh the risk-benefit ratio and at the same time, not dismissing those with multiple mildly raised CV risk factors as not being at increased risk, or turning healthy persons into 'sick' patients based on just a single mildly elevated risk factor. This is where a global estimation of CVD risk is necessary. Once an individual's CV risk is predicted with some degree of certainty, the management can be tailored accordingly, such as when to intensify preventive intervention, when dietary advice should be strict and specific, when physical activity should be intensified and individualised, and when and which drugs should be prescribed to control risk factors.

So what should be included in risk stratification? Obviously age, gender, blood pressure, lipid levels, presence of smoking and diabetes mellitus are important and need to be included in any risk prediction score. Many studies have shown that these risk factors alone contribute and explain about 85% of the population attributable risk for coronary heart disease.[4] Family history of premature coronary heart disease is well accepted to be a risk factor, as it can increase one's risk by as much as 50%. Unfortunately, not all the risk score formulae include this in their derivation of the score. Other newer and more novel CV risk factors have been identified and they include the following: obesity/metabolic syndrome; physical inactivity; left ventricular hypertrophy; atrial

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fibrillation; pulse rate; apolipoprotein B/Lp(a); high-sensitivity C-reactive protein (hs-CRP); fibrinogenaemia; hyperuricaemia; increased serum creatinine; microalbuminuria/albuminuria; social deprivation/low socioeconomic status; total coronary calcium score; and carotid intima thickness.

The addition of these factors in routine risk prediction has not improved the accuracy to any significant degree when compared to just using the traditional risk factors.[5] They also have yet to be shown to improve CV morbidity and mortality when treated. Future research would have to be made available before these novel risk factors can be included, especially as some of these risk factors are difficult and expensive to measure. However, determining some of these risk factors in an individual, especially in a person in the intermediate risk range can have an added benefit, as it may re-classify someone with intermediate risk as high risk. Many tools for CVD risk assessment have been developed over the past two decades. Table I shows the development of these algorithms in chronological order. Table II summarises the characteristics of the different CVD risk prediction models, followed by some details about the algorithms.

Table I. Chronology of cardiovascular disease risk prediction scores.

Year	Name of risk chart
1991	Framingham Heart Study CHD Prediction: + LVH
1998	Framingham Coronary Heart Disease Risk Prediction
1999	British Joint Societies CHD
2002	PROCAM (Munster)
2003	SCORE
2004	British Joint Societies CVD
2004	WHO/ISH
2007	ASSIGN
2007	QRISK 1
2008	QRISK 2
2008	Framingham General CVD Risk Prediction

FRAMINGHAM CORONARY HEART DISEASE RISK PREDICTION

The first prediction score to be developed is the Framingham Coronary Heart Disease Prediction Score,[6,7] which predicts fatal and non-fatal coronary heart events. Lately, the Framingham general CVD risk profile for primary care was developed, and this included not only cardiac events but also other CV events like stroke, both fatal and non-fatal.[8]

The Framingham Heart Study (FHS) was first initiated in 1948 by what was then known as the National Heart Institute (now known as the National Heart Lung and Blood Institute [NHLBI]) as a project in health research.[9] This was in response to the steadily increasing death rates from CVD, which became an epidemic in the United States (USA). Furthermore, little was known then about the general causes of heart disease and stroke.

Framingham is a town in Massachusetts, USA, where the community is very stable, with little migration. The aims of the FHS then were to identify the common factors or characteristics that contribute to CVD by following its development over a long period of time in a large group of participants who were free from previous CVD (coronary heart disease [CHD] or cerebrovascular accident [CVA]). In 1948, the first FHS cohort was enrolled. Since 1948, detailed medical history, physical examination and laboratory tests were done every two years. In 1971, a second generation called the Offspring Cohort, comprising 5,124 adult offsprings, was enrolled. In April 2002, the third generation, the grandchildren of the Original Cohort, was enrolled in order to study the genetic factors and CVD.

The FHS gave us much of what is known today about the relationship of CV risk factors and CVD, in particular CHD. The original cohort from which the FHS was derived consisted of the following characteristics: (a) The total number of participants was 5,345, of which 46.5% were men; (b) The participants were aged 30–74 years; (c) Baseline data was collected in 1971–1974, which was the data from the 11th examination of the Original cohort and the first examination of the Offspring Cohort; (d) The follow-up was for 12 years; (e) The participants with existing CHD were excluded from the study; (f) A similar protocol was used throughout, with two-yearly examinations conducted by the researchers; (g) All hospital or clinics records of CHD events were reviewed; and (h) All CHD events were validated and adjudicated by two independent researchers. The CV risk factors in FHS included age, gender, systolic blood pressure (SBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, smoking and diabetes mellitus. The outcome consisted of charts that predicted CHD only, including fatal and non-fatal myocardial infarction (MI) as well as angina and coronary insufficiency; separate charts that were developed for men and women; and separate charts that were based on total or low-density lipoprotein (LDL) cholesterol.

Some of the limitations and criticisms of the FHS score include the small number of participants, the predominance of a white population in the USA, the small number of events (383 in men and 227 in women), the exclusion of family history of CHD and body mass index, not taking into account any current treatment with anti-hypertensives, and finally, that the FHS predicts only CHD.

Table II. Characteristics of common cardiovascular disease risk prediction algorithms.

	FHS[6,7]	PROCAM[20]	WHO/ISH[28,29]	SCORE[22,23]	ASSIGN[30,31]	FHS Gen[8,19]	QRISK[32]
Year	1998	2002	2003	2003	2007	2008	2008
Age (yrs)	30–74	40–65	40–70	45–64	30–74	30–74	35–74
No.	4,545	4,849	NA	205,178 Datasets of 12 European countries	12,000	8,491	1.2 million
Gender	Male and female	Male only	Male and female	Male and female	Male and female	Male and female	Male and female
Year recruited	1971–1974	1985	NA	Variable;1972–91	1980–1990	1968–75, 1984–87 Offspring Cohort	1995–2007
Follow-up (yrs)	12	10; Initial exam repeated after 6–7 yrs;. followed up by own doctor	NA; based on mortality, prevalence and incidence rates of regions	Variable	Scottish Heart Health Study, followed up till 2005	12	Variable; 0–12; median follow-up is short
Risk factors	Age, gender, DM, SBP, smoking, T-chol or LDL-chol, HDL-chol	Age, SBP, HDL-chol, LDL-chol, Tg smoking, DM, FH, CHD	Age, SBP, smoking, chol, HDL-chol; separate charts for no lipids and for DM	Age, gender, smoking, SBP, chol or T-chol/ HDL ratio	CVD RF, f/h CHD + social deprivation	CVD RF + treated BP	Age, gender, smoking, SBP, T-chol/HDL ratio, LVH, BMI, FH CVD, deprivation, current anti-HT medication; missing data
Outcome	Fatal and non-fatal CHD (including angina)	Fatal and fatal MI (angina not included)	Fatal and non-fatal MI and Stroke	Only Fatal CVD; 2 sets of charts for low and high CVD risk regions	CVD: fatal and non-fatal events, CHD, stroke	CHD (coronary death, angina, coronary insufficiency), cerebrovascular events (all strokes and TIA), PAD, HF	All CVD: MI, CHD, stroke, TIA
Events validated	Records reviewed for morbidity and mortality	Death certificate and hospital records reviewed for morbidity and mortality	No actual events	No; based on records by doctors	No review or validation; based on reports	Prospective, 2 yearly follow-up; validated events by neurologist or cardiologist	No; data from GPs computerised records database
External validation	Yes	No	No	Yes	No	No	Internal validation only

FHS: Framingham Heart Study; PROCAM: Prospective Cardiovascular Munster Score; WHO/ISH: World Health Organization/ International Society of Hypertension; SCORE: Systemic Coronary Risk Evaluation; ASSIGN: Risk Score Based on the Scottish Heart Extended Cohort; FHS Gen: Framingham Heart Study General Cardiovascular Risk Profile; QRISK: Cardiovascular Disease Risk Score Based on the British QRESEARCH database.

The strength of the FHS is the prospective nature of the study, which was conducted at a single centre using a similar protocol throughout the study. Additional strengths include the frequent two-yearly examinations conducted by researchers, as well as the validation and adjudication of events by independent researchers and specialists. The greatest strength of the FHS is that it was a prospective study conducted at a single centre during the period 1971–1986, an era when most of the patients were not on any medication. In fact, the first calcium channel blocker was only licensed in 1980, the first angiotensin receptor blocker, in 1981, and lovastatin, the first statin, only in 1987. Furthermore, while 32.6% of the FHS cohort had hypertension, only 6.8% were on treatment. Hence, it is conceivable that the majority of the participants were not on any active medication.

Any active treatment would have altered and lowered the outcome risk. If the purpose of generating a risk score is to predict the level of risk and hence, the indication for active intervention, then it is not logical to use a risk score that is derived from participants who are already on treatment. Many of the more recently derived algorithms like QRISK were derived from patients on treatment. Thus, when compared to the FHS score, the Framingham risk score naturally over-predicts the risk in patients who are already on treatment.

In spite of the limitations, the FHS has been validated in some populations and found to be quite effective. What must also be remembered is that the FHS risk equation was developed during the peak incidence of CVD in the USA, and it has been found to perform well in populations with similar CHD rates, such as Caucasians, African-

Americans and Koreans.[10-12] The FHS risk equation may, however, overestimate risk by up to 50% in contemporary northern European populations such as those in Italy, France and Spain, where the incidence of CVD is lower.[13-15] It has also been found to overestimate risk in British men[16] and in a Chinese population,[17] where the background risk of CVD is also lower. However, it has worked well with recalibration. It also overestimates risk in elderly men, but not in elderly women.[18]

To address the issue of the FHS predicting only CHD, the FHS developed a new General CVD Risk Profile for use in primary care in 2008[8,19] using the same methodology but including not only the 11th examination of the original cohort (1968–1971) but also the first (1971–74) or third examination (1984–87) of the Offspring cohort. The number of participants hence increased to 8,491. This prediction algorithm included different points for treated or not-treated SBP. This new general CVD risk score would need to be validated further to determine its utility.

PROSPECTIVE CARDIOVASCULAR MUNSTER (PROCAM) SCORE

The PROCAM score,[20] occasionally referred to as the Munster score, was developed in the town of Munster, Germany. The data was drawn from a cohort of 20,000 people aged 16–65 years from 1979 to 1985. However, the original score was developed based on 5,389 men only from the said cohort. There were a total of 325 CHD events, which is even fewer than those among the FHS male cohort. Like the FHS, this score only predicted CHD mortality and morbidity. As women were not included in the development of the score, it was proposed that the score for women should be the multiple of a factor of 1.2 of the men's score. The advantage of this score was that it included family history of CHD and triglycerides. The PROCAM score has recently been updated and the score now predicts MI and stroke as well.[21]

SYSTEMATIC CORONARY RISK EVALUATION (SCORE)

Recognising that the FHS may not work well for countries in Europe with differing background rates of CVD, the Europeans developed a score encompassing not only CHD but other CV events. SCORE[22,23] was derived from 12 different European cohort studies that were made up of multiple sub-cohorts, with varying recruitment time, half of which were conducted in the 1980s. The advantage was the population-based cohorts with a large number of participants (250,000). The risk factors included age, gender, SBP and smoking. Diabetes mellitus was not included in the risk score, not because it was not an important risk factor, but because the records were poorly collated, as these cohorts, unlike the FHS, were not set up specifically to study CVD. This score predicts only fatal CVD events, which is not consistent with other therapeutic trials which predicted both fatal and non-fatal events. Only fatal events were used as the outcome because not all the data regarding non-fatal events was available. In fact, some sub-cohorts did not study CVD at all, and hence, no such data was collected.

Trying to convey risk as a fatality to subjects who are asymptomatic may be inappropriate and may even have a negative impact. Furthermore, a risk score > 5%, which is considered high risk by the SCORE algorithm, is not in concordance with that used by other scores, where only a risk > 20% is considered high risk. This may further confuse the subjects. Another disadvantage of using this prediction chart outside of Europe is the dilemma one would face regarding the kind of chart to be used for a patient; the low or high-risk chart. To make that choice, one needs to know the background CVD risk of that country, but this data is not readily available or accurate. The authors have proposed that the risk for diabetics is twice that for men and four times that for women of the SCORE risk. Other limitations of the SCORE were as follows: (a) It can only be used for people aged 40–65 years, as the cohorts did not include people out of this age range; (b) The fatal events were not reviewed or validated, but were based only on reports; (c) It has not been validated as extensively as the FHS in other populations; and (d) It was found to overestimate risk in the Chinese population.[24]

JOINT BRITISH SOCIETIES FOR CVD RISK

This risk prediction chart developed by the Joint British Societies (JBS)[25,26] included the following risk factors: age, gender, SBP, total cholesterol, HDL cholesterol and smoking. The chart did not use a specific age but produced three age categories, i.e. < 50 years, between 50–60 years and > 60 years. It predicts fatal and non-fatal CVD. Diabetes mellitus was not included in the score, as diabetics were deemed to have high risk of > 20%, and thus did not need to be scored. The JBS score was in fact based on the FHS equation. However, it has been validated in a small (n = 691) British population in primary care practice, and found to work better than the FHS. It also had high specificity (98.7%, 95% confidence interval [CI] 97.5%–99.5%) and good sensitivity (84.7%, 95% CI 71.0%–93.0%).[27] This chart's limitation may be similar to that of the FHS, as it was based on the FHS equation.

WHO/ISH CVD RISK PREDICTION CHARTS

The World Health Organization, in collaboration with the International Society of Hypertension,[28, 29] developed a risk chart in 2003/04 to serve regions without their own charts. Recognising the fact that in low-resource countries, serum lipid testing was often not conducted, these charts did not include serum lipid measurements. To develop these charts, hypothetical cohorts for each region were drawn up. These charts were then derived based on the prevalence of the means of CVD risk factors and the CVD event rates of the region or country. The calculation was then extrapolated to a ten-year risk. Like other risk charts, age, gender, SBP, total cholesterol and smoking were included. Charts for instances where no cholesterol result is available were also developed. Separate charts were used for diabetics and non-diabetics. These charts predict both fatal and non-fatal CVD events, in particular, MI or stroke. There are different charts for different regions of the world.

ASSIGN SCORE

The ASSIGN score[30,31] is based on outcomes in the Scottish Heart Health Extended Cohort study conducted in Scotland from 1984 to 1987 and in North Glasgow in the years 1989, 1992 and 1995. It is a random sample of 6,540 men and 6,757 women aged 30–74 years. The same risk factors as FHS were included, but like PROCAM, it included family history of CVD and social deprivation as an additional new variable. Endpoints for the ASSIGN score were fatal and non-fatal CVD. However, as Scotland has a different and higher background risk for CVD compared to the rest of the United Kingdom (UK), this score is perhaps best suited for use in Scotland, and it is recommended as such.

QRISK AND QRISK 2

The first QRISK algorithm was developed using a population-based clinical research database in the UK.[32,33] Two cohorts were extracted from this database: A Derivation Cohort consisting of 1.28 million patients registered at 318 general practices who were recruited from January 1, 1997 to April 1, 2007. These patients were aged 35–74 years, and were free of diabetes mellitus and CVD; and a Validation Cohort consisting of 0.61 million patients from 160 practices. The risk factors included were age, gender, smoking status, SBP, total/HDL cholesterol ratio, family history of CHD in first degree relatives < 60 years, area of deprivation, treatment with anti-hypertensive agents and body mass index (BMI). This score predicts fatal and non-fatal CVD, i.e. MI, CHD, stroke and transient ischaemic attacks.

Using the validation cohort, it was found that the FHS over-predicted by 35%, the ASSIGN score by 36% and the QRISK by 0.4%. However, the QRISK also under-predicted risk in 12% of the cohort. The weakness of the QRISK algorithm is that while BP and BMI recordings were good, cholesterol uptake was poor, with less than 30% having their serum cholesterols measured. Furthermore, HDL cholesterol measurements only became available in 2003. As such, up to 75% of the subjects had one or more missing value, and hence, the missing values were arbitrarily computed. Other limitations included: (a) Events not validated but based on doctors' diagnosis on computer records; (b) Patients included at different times; (c) Not all patients had ten-year follow-ups or contributed ten years' worth of data; (d) The median follow-up time was relatively short, especially when compared to the FHS and ASSIGN; (e) Only 300,000 (23.3%) patients had ten-year follow-ups; and (f) The score was not validated in populations other than the British.

The QRISK 2,[34] as the name implies, is a study similar to QRISK. Like QRISK, it is based on a prospective open cohort, whose data was routinely collected by general practitioners to form the national QRESEARCH database. Data was drawn from 531 practices in England and Wales, comprising 2.3 million patients aged 35–74 years who were seen from January 1, 1993 to March 31, 2008. The selected subjects included 2.2 million Caucasians, 22,013 South Asians, 11,595 black Africans, 10,402 black Caribbeans and 19,792 Chinese, Asian and other ethnic groups. Besides the same limitations, as seen with QRISK, this score has also not been validated in other populations except in British minorities.

OTHER CVD RISK PREDICTION ALGORITHMS

There are many other less well-known risk charts, including: (a) Reynolds Score, which is based on the Women's Health Study. This score includes the usual risk factors plus hs-CRP and family history.[35] As this score is drawn from women's data, it would not be applicable for men; (b) New Zealand Score,[36-38] which is also based on the FHS equation; (c) CUORE equation, which was developed in Italy for a low coronary incidence population;[39] (d) MUCA ischaemic CVD risk model developed for the Chinese population;[40] (e) A multi-regression model involving CRP that was developed in Japan;[41] (f) A recalibrated Framingham, which was tested in Thailand;[42] (g) Risk Score model from the Busselton Heart Study in Australia;[43-45] and (h) Assessment of Total CV Risk Engine according to the UK Prospective Diabetes Study, a prediction score for diabetics.[46] It is apparent that all the above risk

score charts have their own inherent advantages and disadvantages. They measure different CV outcomes and some predict fatal events only. They were also done at different times, included different age ranges, had different values for risk definition, and some were even gender-specific.

It is important to remember that CVD risk may be higher than indicated in the charts, especially in patients with raised triglycerides, low HDL cholesterol, raised CRP, homocystein, apolipoprotein B, Lp(a), dysglycaemia, impaired glucose tolerance or impaired fasting glucose and microalbuminuria. It may also be higher than indicated in the charts of individuals who are undergoing anti-hypertensive treatment, women with premature menopause, those approaching the next age category, as well as in those with obesity, a sedentary life style and a family history of premature CHD. It also tends to underestimate risk in those with left ventricular hypertrophy or retinopathy (Grade III and IV), those with persistently high total cholesterol, LDL-cholesterol, total/HDL cholesterol ratio or high BP, Type 1 or 2 diabetes mellitus patients with overt nephropathy or other significant renal disease, and patients with known renal failure, renal impairment.[36,47,48]

It must also be noted that risk charts have different accuracies in different populations. They tend to over-predict in low-risk populations and under-predict in high risk populations.[49] While social deprivation has been built into some of the prediction scores (e.g. ASSIGN, QRISK), ethnicity has not. We need to take these into consideration when addressing and managing an individual's overall CVD risk. There are situations when risk prediction is not necessary, and these include patients who have established CV events, or have persistently elevated BP (> 160–170/100–105 mmHg) or marked elevations of total cholesterol ≥ 8 mmol/l, LDL-cholesterol ≥ 6 mmol/l or a total /HDL cholesterol ratio > 8, type 1 or 2 diabetes mellitus patients with overt nephropathy or other significant renal disease, and patients with known renal failure or renal impairment.

All risk prediction algorithms have their limitations. While some may have low sensitivity but good specificity, others may give a good estimate or order of ranking, but over- or under-predict absolute risk. Some risk prediction algorithms can differentiate between low and high risk. It should also be remembered that the decision to treat with drugs should be based on repeated assessment of risk factors and that risk estimates are based on untreated levels of BP and cholesterol. In those already receiving treatment, it can only be used as a guide.

It has been argued that the currently available risk prediction algorithms may also not be directly applicable to local or regional populations who may not share the same CV risk characteristics as the cohorts from which the scores were derived. Thus far, New Zealand,[36-38] Australia,[43-45] China[40] and Hong Kong[50] in the Asia Pacific region have developed their own risk prediction charts, but some of these charts are still based on the Framingham equation, albeit with some recalibration. These charts have not been validated in other Asian countries. Therefore, if they were used in other countries in the Asia Pacific region that do not have their own charts, they will suffer the same inherent problems similar to the more established charts. This is due to the differing mean levels (or prevalence) of cardiovascular risk factors and the differing background incidence of CVD events.

Ideally, each country should have its own risk score, but this would be an expensive exercise that takes a long time to develop. Perhaps all that some of the algorithms need is some recalibration. The Asia Pacific Cohort Studies Collaboration has shown that such recalibration of the Framingham risk prediction tool is likely to estimate future CV risk with similar accuracies in Asian populations as tools developed from data on local cohorts.[51] Hence, in the interim, it is worthwhile to be familiar with some of these scores, select one that is most appropriate for the patient and discuss treatment options based on the estimated risk.

Finally, the choice of prediction model to use on a patient depends on how good a fit the model will be, the background risk of CVD in that particular population and whether the charts can be validated or recalibrated for local use. Take for instance, a 65-year-old non-diabetic male patient who is a non-smoker, with BP 150/90 mmHg, total cholesterol 5.6 mmol/l and HDL cholesterol 0.9 mmol/l. Superficially, his CV risk factors do not appear to be alarming, but his predicted risk, as shown in Table III, reveals a high risk for both fatal and non-fatal CVD and/or CHD over the next ten years, regardless of which prediction model is used. Therefore, while the absolute

Table III. Comparison of a ten-year risk for CVD using different risk prediction models.

Risk prediction model	Risk (%)
SCORE	
Low-risk region	9
High-risk region	16
FHS CHD	31
FHS CVD	34.2
WHO	30
BNF/JBS	30.4
ASSIGN	26.8

risk predicted may differ with the different models used and may over- or underestimate the absolute risk, they all point toward the same direction of risk.

CONCLUSION

It is important to use a model that one is most familiar with, and to use it correctly and in the right context. Failure to conduct a global cardiovascular risk assessment by not using any of these tools may result in overlooking patients who are at a seemingly low risk, and hence, missing an opportunity for intervention.

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