Risk Assessment in the Prevention of Cardiovascular Disease in Low-Resource Settings: Lessons for practitioners in Nigeria

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ABSTRACT

INTRODUCTION

Cardiovascular disease prevalence is increasing in low and middle-income countries, which bear around 75-80% of the global burden. Total cardiovascular disease risk assessment is key to prevention.

METHODS

A search of studies published between 1990 and 2013 was conducted. Medline database, PubMed and World Health organization report sheets were used.

RESULTS

The ideal risk prediction tool is one that is derived from the population in which it is to be applied. In the absence of national population based cohort studies in sub-Saharan African countries like Nigeria, there is no tool that is used consistently. Regardless of which one is adopted by national guidelines, routine consistent use is advocated by various CVD prevention guidelines.

CONCLUSIONS

In low-resource settings, the consistent use of simple tools like the WHO charts is recommended as the benefit of a standard approach to screening outweighs the risk of missing an opportunity to prevent CVD.

KEYWORDS

Cardiovascular diseases; risk assessment; risk markers; cardiovascular disease prevention

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INTRODUCTION

Cardiovascular disease is a progressive consequence of atherosclerosis that begins early in life with a long latency period before the first manifestation. Cardiovascular disease is the cause of death in about 16.7 million people around the world and this is projected to increase to 24 million deaths by 2030. In Europe, over 4.3 million deaths annually are due to CVD, half of which is from coronary heart disease (CHD) and a third from stroke. CVD therefore imposes a considerable burden on the economy as it costs the European Union about €192 billion annually. Seventy five percent of the CVD burden occurs in low and middle-income countries. In Nigeria although CVD lags behind infectious disease as the commonest cause of death, it accounts for higher age-specific mortality when compared to developed countries.

The underlying risk factors for CVD are similar worldwide as the INTERHEART study showed that nine modifiable risk factors (smoking, low consumption of fruits and vegetables, lack of regular physical activity, abdominal obesity, hypertension, abnormal lipids, diabetes mellitus, and stress) accounted for more than 90% of the risk for incident myocardial infarction.

The increasing age of the population in addition to the rising prevalence of obesity and diabetes (especially among ethnic minorities), are important factors that drive up the prevalence of CVD. Although improved treatment modalities reduce mortality from CVD, the index presentation may be with sudden death or for those who survive an event, long-term disability. Furthermore,

majority of individuals with CVD are asymptomatic therefore, preventive measures remain mandatory.

In order to prevent CVD in an appropriate and cost-effective manner, the total-risk approach is recommended. This involves the assessment of an individual's risk of developing CVD, taking into account several risk factors that may be present. Treatment to reduce the risk is then instituted above a pre-defined threshold that is considered high-risk. It represents a paradigm shift from the traditional method of screening for and treating single risk factors. This is because moderate levels of several risk factors that interact multiplicatively confer a higher absolute risk of CVD on an individual than a markedly elevated level of one risk factor. Moreover, assessments based on total risk leads to better CVD prevention as was shown in a review of randomized controlled trials (RCT) where treatment benefit in terms of absolute risk reduction was a function of an individual's pre-treatment total CVD risk rather than the specific level of any single risk factor. Several tools for estimating total cardiovascular risk are available and recommended by national and international guidelines. They are available as paper charts or online calculators with the latter incorporating more variables. Risk assessment is a key component of national policies like Putting Prevention First in the United Kingdom. In developing countries in sub-Saharan Africa like Nigeria, the situation is different. There have been no population-based cohort studies done; information about cardiovascular risk factors are obtained mostly from hospital-based and small community cross-sectional studies. As a result the effect of these risk factors on cardiovascular outcomes in this environment remains largely unknown. Furthermore there are no national guidelines on risk assessment at this time therefore in practice clinicians assess risk mostly from guidelines produced in developed nations. This articles aims to review the various tools available to assess and predict cardiovascular risk and highlight areas that can be applied to low-resource settings.

Risk Estimation, Advantages And Disadvantages of the Risk Estimation Tools

Risk estimation aids a clinician to identify individuals at high multifactorial risk for CVD and tailor the intensity of interventions to baseline total cardiovascular risk. A risk assessment tool that has been validated and evaluates relevant non-modifiable and modifiable risk factors is required to calculate the absolute risk. Absolute risk is determined by the synergistic effect of all the cardiovascular risk factors present and is defined as the probability that an individual will have a cardiovascular event in a defined period, usually 10 years. Individuals at high absolute risk benefit the most from intervention. The tools are not exactly accurate as other variables like diet and exercise are not included so it remains important to individualize any interventions.

Risk assessment of an individual starts with identifying his/her risk factors, some of which may be modifiable. These factors, their implications for health and the recommended goals should be discussed with them. The risk assessment tools (in table 1) available to estimate absolute risk vary slightly in the risk factors they incorporate therefore, the calculated absolute risk will vary. Jackson et al. pointed out that single risk factors like blood pressure and cholesterol on their own have a minor effect on a patient's absolute risk but in the presence of others can have a major effect. In the Multiple Risk Factor Intervention Trial, at all levels of BP and cholesterol, an additional risk factor like smoking multiplied the absolute CVD risk even further.

The use of equations to estimate CVD risk has been shown to be better than clinical judgment alone. The tools include:

- Joint British Societies 2 (JBS2) risk calculator (based on the Framingham risk score)

- Pooled Cohort Equations
- World Health Organisation (WHO) charts
- SCORE (Systematic Coronary Risk Evaluation)
- QRISK2 risk calculator
- QRISK Lifetime cardiovascular risk calculator
- ASSIGN score (Scotland only)

JBS2

The JBS2 guidelines recommend risk assessment with the JBS2 cardiovascular risk prediction chart or calculator modeled on a Framingham function which is based on data derived from middle class white Americans in the 70's to 80's. Its advantages as a well established model, has been validated in different populations and includes a set of core risk factors i.e. age, gender, smoking, total cholesterol: high-density lipoprotein cholesterol ratio and blood pressure while excluding diabetes. Diabetics are considered high-risk and do not require risk assessment. An important weakness of this risk model is that it omits ethnicity. Although the risk can be adjusted by multiplying with a constant e.g. 1.5 for South-Asian origin but the various South-Asian populations differ in their risk for CVD. The electronic calculator incorporates these variables. In addition it assesses the risk of coronary heart disease alone and does not encompass other CVD such as stroke. Currently in Europe, Framingham based risk scores overestimate risk as CVD mortality is declining especially in people who reside in affluent areas. The National Institute for Health and Clinical Excellence recently withdrew its recommendation to use Framingham equations as the tool of choice for risk assessment.

Pooled Cohort Equations

These are sex- and race-specific Pooled Cohort Equations developed from multiple, community based large cohort studies in the United States to estimate the 10-year and lifetime risk for 'hard' atherosclerotic CVD events for African-American and White men and women 40 to 79 years of age. The data from which this tool was derived is mostly recent from the 1990's. The variables included in this equations are age, total and HDL-cholesterol, systolic BP (including treated or untreated status), diabetes, and current smoking status. The end-point of hard atherosclerotic events is defined as the first occurrence of nonfatal myocardial infarction or CHD death, or fatal or nonfatal stroke. Patients are considered to be at "elevated" risk if the Pooled Cohort Equations predicted risk is $\geqslant$ 7.5%. This equation is proposed to replace the traditional Framingham risk equation. Its inclusion of stroke as an endpoint is advantageous because in groups like women and African-Americans, stroke occurs earlier than heart attack. Thus this is appropriate for assessing their risk. This tool is validated for use only in Caucasians and African-American blacks so outside these populations it may not accurately predict CVD risk. In validation studies using three separate cohorts, this equation was found to overestimate risk only in high-risk patients who would require statin therapy regardless. In lower risk patients in order to buffer the effect of risk overestimation, the treatment threshold is 7.5% as opposed to 5%, which is the level of risk in clinical trials above which statin therapy is beneficial.

WHO

The World Heart and Stroke Forum classify risk factors into major, underlying and emerging. They suggest that differences in the underlying risk factors (obesity, poor diet, physical inactivity, family history of premature CVD, ethnicity, stress) affect baseline population risk, and may account for the variability of absolute risk predicted by the major risk factors. Different regions in the world differ in their distribution of CVD risk factors and in most low and middle-income countries (LMIC) there are no population derived cohort data. The risk factors considered include age, systolic blood pressure, smoking status, blood pressure treatment status, history of diabetes mellitus, and cholesterol. In resource-poor settings where lab tests are not readily available,

another chart for risk prediction was provided which excluded cholesterol. Due to the absence of population derived cohort data, the prediction charts for each sub-region was developed using the modelling approach. The modelling method by which the charts were derived makes it a weaker risk estimation system moreover it has not been compared with any of the standard prediction rules nor validated in any cohort. Having said that however, a study by Gaziano et al., compared the use of non-lab based data with lab-based data to estimate the 10-year risk of incident cardiovascular events (myocardial infarction, heart failure, stroke, angina) in participants in the National Health and Nutrition Examination Survey (NHANES) study. Using the same risk factors in the WHO charts with the substitution of BMI for cholesterol in the non-lab based model, they found a very close correlation between the two models in risk prediction. Their findings suggest that the WHO charts may be used with less anxiety to predict risk in low-resource settings. In these settings multiple factors affect the feasibility of CVD prevention apart from poorly funded healthcare. Distances patients travel to access healthcare may make it impossible to present early in the day for a fasting blood test so the used of this non-lab based model to predict CVD risk in one clinic visit remains an attractive choice in these settings.

However, the WHO charts do not include factors like obesity and family history of premature CVD and therefore has the potential to underestimate an individual's actual risk. The specific threshold for intervention is based on the available health care resources in each sub-region.

SCORE

The SCORE project is a risk scoring system derived from pooled cohort studies across 11 European countries and is recommended by the European guidelines on CVD prevention. Based on a larger, more current cohort, it is more likely to reflect the baseline CVD risk across Europe better than the JBS2 calculator. Its other advantages include that it is an easy tool to use, is based on the European guidelines, and depicts the relative contribution of modifiable risk factors in a graphical format. It also shows how risk increases with age and the relative risk chart helps to illustrate how a young person with a low absolute risk may be at a substantially higher and reducible relative risk. It has a simple chart format, and charts have been shown to enhance the use of risk assessment tools in clinical practice. In addition, its inclusion of the integer value as well as color codes for the different levels of risk offers an advantage over charts like the JBS2 that are color coded only. In developing this SCORE, the 10-year risk of death was the end-point allowing ease of ascertainment across the various cohorts used. A disadvantage of this is that in an asymptomatic individual, conveying their risk as a fatality might have a negative effect. Besides the fatal events used as the outcome were based on reports and not validated. Also, excluding the risk of morbidity might be a disadvantage since most CVDs are non-fatal events.

QRISK2

The QRISK2 was derived from a large cohort from the primary care database (QRESEARCH) in England and Wales. It has been validated in various cohorts and in an external validation study using The Health Improvement Network database, it was better than the Framingham-based scores in estimating risk among individuals in a UK population. Ethnicity influences cardiovascular risk so using the QRISK2 may help to reduce health inequalities that arise when people are misclassified using tools that exclude ethnicity. QRISK2 works over a wider age range than the JBS2 and SCORE calculators so this is an added advantage. The additional variables in QRISK2 (table 1) are easily obtained and their inclusion improves its ability to discriminate between people who will develop the endpoint from those who will not. Though there is little improvement in the function of a model upon addition of variables after conventional risk factors, D'Argostino and colleagues suggest that if the cost of

obtaining new variables is low, it may be well worth including in the prediction model. In addition, as the population changes, this tool can be regularly updated improving its durability.

Some disadvantages of this algorithm include the non-standardization of outcome measurements which were based on doctors diagnosis recorded on a computer, the baseline risk factors were measured at different times during the observation period and many missing data (e.g. lipids) were included in the analysis. In addition, the inclusion of postcode as a measure of deprivation, may limit the applicability of this tool in areas outside the UK.

QRISK Lifetime

The QRISK lifetime calculator was developed from the QRESEARCH database. Cardiovascular 'life-time risk' estimation has the potential to improve risk prediction as it estimates the absolute risk of an individual developing CVD over their remaining lifetime based on their risk factor profile. With this, younger people who have low or intermediate absolute risk (as age is a key driver of absolute CVD risk), but a high lifetime risk can be identified. Moreover, younger patients have a longer lifetime in which CVD may manifest and earlier intervention may lead to greater benefit. This is because the duration of exposure to a risk factor is probably more important than a 'snapshot' summary of its current level. Its other advantages lie in its potential as a public-health awareness tool as awareness of risk of a disease may lead to better adoption of prevention strategies and the new Joint British Societies guidelines on CVD prevention (JBS3) will focus on this approach. Also when compared to the lifetime-risk of other diseases such as cancer, its huge impact on public health may be better understood. One disadvantage is that its applicability to individual patients is questionable as estimates of lifetime risk represent the average experience derived from large cohorts. In addition, some CVD risk factors e.g. smoking increases the risks of death from non-CVD causes and may in fact reduce the risk of dying from CVD. It only estimates 'hard' endpoints like death and non-fatal MI whereas outcomes like quality of life and disability adjusted life years are becoming increasingly important with better treatment modalities. Furthermore, the purpose of risk estimation is to make a decision on actions to be taken presently and the 10-yr absolute risk estimation identifies individuals who stand to benefit the most from intervention in the short term whereas, lifetime risk may lead to 'over treatment'. This is because most people will have a high lifetime risk for CVD therefore in considering the need for primary prevention, which is the priority in developing countries with an emerging CVD epidemic the lifetime risk alone is not appropriate.

ASSIGN

The ASSIGN score estimates the risk of total CVD (fatal and non-fatal) over 10 years based on a cohort of Scottish people and is recommended by Scottish Intercollegiate Guidelines Network. It was developed as an alternative to the Framingham equations that was inaccurate in estimating risk in their population. The cut-point for intervention is 20% like the JBS2 however it differs from it by including social deprivation, family history of premature CVD and number of cigarettes smoked not just smoking status. It also gives lower absolute values and it has not been validated in a non-Scottish population.

Other methods and markers to estimate CVD risk

Almost half of all CVD deaths occur in individuals at intermediate-risk and a proportion of individual variance in risk remains unexplained. Therefore, there is continued interest in the search for other methods and markers to improve the predictive ability of current risk estimation tools. These include biologic, genetic or imaging modalities. One measure to determine the discriminative ability of a risk prediction model is the C statistic. Values between 0.7-0.8 are considered acceptable and a risk marker requires a large odds ratio or

relative risk to meaningfully increase the C statistic. For new markers to improve the performance of current models, they should be inexpensive, easily measurable and independently associated with CVD. Most new markers correlate highly with traditional risk factors and do not increase the C statistic significantly when added to the existing risk models.

Of all the biologic markers (N-terminal pro-brain natriuretic peptide, homocysteine, fibrinogen, lipoprotein-associated phospholipase 2, etc.), C-reactive protein (CRP) a circulating marker of inflammation has been extensively studied and is the most consistently associated with CHD. It improved risk prediction (as much as lipids) when added to the Framingham score in the Women's Health Study and was useful in reclassifying individuals at moderate risk, but in the British Women's Heart and Health Study it was not associated with CVD and did not improve prediction., One reason for this difference may be that the participants in the former were younger and CRP is a marker of early atherosclerosis. The contribution of ten biomarkers (including CRP) to CHD was assessed in the Framingham cohort. Higher multi-marker scores correlated with major cardiovascular events and deaths but only added modestly to risk prediction based on conventional risk factors. A systematic review concluded that CRP improved risk stratification or reclassification when added to established risk factor-models but in a small and inconsistent manner. The current European guidelines give a weak recommendation for its assessment in individuals at moderate risk to influence clinical decisions.

Family history of premature CVD is an important risk factor suggesting a genetic component to CVD. Genetic abnormalities can affect intermediate phenotypes like cholesterol, or directly influence CVD. However, the relationship between genetics and CVD is complex and individual genes identified in genome-wide association studies to be associated with CVD have small effects. The ability of two genetic risk scores comprising all published single nucleotide polymorphisms, to predict total CVD was tested in participants of the Women's Genome Health Study. The scores were associated with cardiovascular events but did not improve cardiovascular risk prediction beyond traditional risk factors. There is currently insufficient evidence to include them in clinical risk prediction tools.

Imaging modalities enables assessment of subclinical atherosclerosis. Coronary artery calcium (CAC) score detected by computed-tomography scanning indicates the presence of an atherosclerotic plaque in the artery and correlates with the severity of atherosclerosis. In a meta-analysis of four prospective studies with a mean follow-up of 3.6 years, CAC score predicted CHD events after adjusting for established risk factors. Results from the Multi-Ethnic Study of Atherosclerosis, went further to show that adding CAC to a risk model based on the traditional risk factors correctly reclassified 23% and 13% of the participants into high and low-risk categories respectively and this benefit was most in the intermediate-risk group. It is a non-invasive test but the costs and risk of radiation exposure (however minimal) remain significant limitations to its routine use. Vascular ultrasound of the carotid arteries can be used to measure the carotid intima-media thickness (CIMT), characterize atherosclerotic plaques and measure arterial stiffness. As the CIMT rises above 0.9 mm, the relative risk of CVD increases, even after adjusting for traditional risk factors especially in women. Others include the measurement of ankle-brachial index and exercise electrocardiography. While the current European guidelines recommend that these imaging modalities may be reasonable for risk assessment in individuals at moderate risk, the 2013 ACC/AHA Cardiovascular Risk Guideline does not recommend its use for routine measurement in clinical practice for risk assessment for a first ASCVD event., Generally, although new markers may help to

reclassify people at moderate risk above or below a chosen intervention threshold, it remains important to determine the potential treatment impact of reclassification and whether the health benefit of reclassification outweighs the added cost and risks of biomarker measurement as pointed out by Pletcher and Pignone .,

Communicating risk

A vital part of risk prediction is communication. Individuals need to understand the meaning of their calculated CVD risk in order to be motivated to adopt healthy life-changing behaviours and treatments. Risk can be communicated in a sensitive manner using concepts like relative risk, risk age/heart age, rate advancement period and lifetime risk.

The absolute risk of an individual can be compared with that of a person in the same age group but with normal levels of risk factors. This is referred to as relative risk and its enables the individual understand their risk relative to their peers not necessarily as a basis for treatment decisions. In a cluster RCT, risk depicted graphically as relative risk in combination with strategies to modify risk factors positively influenced the behaviour of both the physicians and patients in the intervention arm. Follow up after 6 months showed that they had lower blood pressures and their Framingham risk score was significantly 10% lower compared to those who received usual care. However the appropriateness of recalculating risk after intervention is questionable.

Heart age or risk age is used to determine if an individual, who has a low or intermediate risk will benefit from early intervention. It is the age of a person with the same predicted risk but with all other risk factor levels in normal ranges. The SCORE and QRISK2 calculators give estimates of risk age. Individuals may find it easier to comprehend the concept of having a heart that is several years 'older' than their chronological age and this knowledge may impact on their decision to modify their lifestyle. One published RCT found that among 413 participants, risk perception was closer to actual risk in those randomized to receive their CVD risk expressed as heart age compared to those who got absolute risk as a percentage and the intention to change was mediated by the higher emotional impact it generated. The extent to which these findings are generalizable however is questionable as the participants were recruited online and may not be representative of the average person with CVD risk factors.

Rate advancement period is the difference between a person's current age and risk age on the relative risk chart. This is the average number of years the individual can expect to lose due to the premature onset of CVD. This simple way to communicate risk was shown to be effective in conveying the benefits of quitting smoking in older smokers in a population based cohort study. Lifetime risk has been discussed above.

Table 1. The different risk estimation tools available with their relevant risk factor variables (adapted from: Cooney et al., 2009).

	JBS2	QRISK2	ASSIGN	JES5*	WHO	QRISK Lifetim e
Data	Based on FHS and Framingha m Offspring Study	QRESEAR CH database	SHHEC prospectiv e study	12 pooled prospecti ve studies from 11 European countries	Different method not based on prospecti ve data	QRESEAR CH database
Populatio n and sample type	General population, Framingha m Mass, U.S. Volunteers	Health records of general practice attendees-not random	Random sample from general population in Scotland	Random samples from general populatio n, some occupatio nal cohorts	Not applicabl e	Health records of general practice attendees-not random
Sample size	3,969 men 4.522 women	2.29 million	6,540 men 6,757 women	117,098 men 88,080 women	Not applicabl e	2.29 million
Calculates	10-year risk of CVD events, Risk age	10-year risk of CHD, stroke and TIA	10-year risk of CVD events	10-yr risk of CVD mortality	10-year risk of CVD events	CVD risk over a person's remaining lifetime
Age (years)	30-75	30-84	30-74	40-65	20-75	30-84
Variables	Age, sex, SBP, DBP, TC, HDL TC/HDL, TG Smoking, Glucose, Central Obesity S.A origin FHx, LVH	Sex, age, TC/HDL, SBP, smoking status, diabetes, area-based index of deprivatio n, family history, BMI, anti-hypertensi ve	Current age Gender FHx Diabetes Cigarettes smoked daily SBP TC HDL Scottish postcode	Age Gender Smoking SBP TC HDL	Age Gender Smoking SBP ±TC Diabetes	Sex, age, TC/HDL, SBP, smoking status, diabetes, area-based index of deprivatio n, family history, BMI, anti-hypertensi ve

*the total risk is for fatal CVD; AF- atrial fibrillation; BP- blood pressure; CHD- coronary heart disease; CKD- chronic kidney disease; CVD- cardiovascular disease (heart attack, angina, stroke or transient ischaemic attack) DBP- diastolic blood pressure; FHS- Framingham Heart Study; FHx- family history of premature CVD; HDL- high density lipoprotein cholesterol; JBS- Joint British Societies; LDL- low density lipoprotein cholesterol; NICE- National Institute for Health and Clinical Excellence; S.A origin- South Asian origin; SBP- systolic blood pressure; SHHEC- Scottish Heart Health Extended Cohort; SIGN- Scottish Intercollegiate Network; RA- rheumatoid arthritis; TC- total cholesterol; TG- triglyceride; TIA- transient ischaemic attack.

CONCLUSION

The overall objective of the risk assessment strategies discussed above is reducing the risk of CVD. It enables clinicians identify and stratify individuals at risk for CVD and aids communication with the individual to help them understand the importance of lifestyle modification and drug therapy. Any of the validated tools can be used but they differ in various ways like the methods by which they were derived, variables included and defined endpoints. However, they are all based on the same principle and using them routinely in practice is more important than decisions regarding which tool to use. Region or country specific tools derived from cohort data are ideal but in developing countries like Nigeria without cohort data, the consistent use of either simple lab-based or non-lab based tools like the WHO charts remains the best choice as the benefit of a standard approach to screening outweighs the risk of missing an opportunity to prevent CVD.

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