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Original Research Article

Prospective, longitudinal, cohort study for assessment of vascular ageing among adults of urban and rural area of Central India: Research Protocol

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ABSTRACT

Background: Considering the complex interaction of risk factors in causation of CVD; assessment of vascular ageing among the high risk group through non-interventional statistical models was useful in controlling CVD. While, many CVD risk assessment models were especially designed for application in the specific population or region such as SCORE scales for Europeans, ASSIGN scores for people of Scotland. The Framingham Risk Score were modified, validated and used in several countries. Though Indians have significantly higher predilection for CVD, no indigenous scores were developed or validated to assess the CV risk. The objective of the study were to determine vascular age of the study participants using Framingham risk prediction model, to assess its relationship with development of cardiovascular disease and to develop, validate and compare cardiovascular risk prediction model based on the follow up observations of the study participants.
Methods: Community based cohort study will be conducted in large urban and rural population aged 31-60 years of among those who have no evidence of CVD. The study population will be followed up for three years and will be assessed for development of CVD. The vascular age will be determined using Framingham Risk Scores. Based on the risk factors associated with occurrence of CVD during the study period, the risk prediction model will be designed and tested for validity and accuracy.
Results: The newly developed CVD risk prediction will be more accurate in assessment of CV risk among the study subjects.
Conclusions: The newly developed and validated CV risk prediction model specific for Indians may be one of the first prospective CV risk assessment cohort study.

Keywords: Cardiovascular risk prediction model, Indian cohort, Validation

INTRODUCTION

Vascular ageing is a complex senescence process occurring as a consequence of natural physical stress and fatigue that could account for the major physical changes seen in elderly such as dilation and stiffening of the arterial wall mainly due to content of elastin and collagen in the vessel wall.[1] Vascular ageing is defined as changes in mechanical & structural properties of vascular wall, leading to the loss of arterial elasticity and reduced arterial compliance.[2] Currently vascular ageing being the only method to predictive assessment of atherosclerosis in major arteries. Vascular ageing can be assessed by direct measurement of Intima-Media thickness, pulse

wave velocity or the arterial augmentation index, measurement of different biomarkers of endothelial dysfunction, measurement of telomere length in the peripheral blood cells.[3] All these methods suitably advisable for individual screening purpose, lack predictability of implicated cardio-vascular event. Evolvement of screening methods based on epidemiological and statistical models being more commonly utilized based on large prospective population trials (such as Framingham Heart Study) which were applicable for different ethnic and geographically versatile populations with reasonable predictive accuracy. These risk factors interact complexly and in a multiplicative manner in causation of CVDs. Though there was complex clustering of the risk factors, epidemiological and statistical methods succeeded in formulating various models in explaining the mathematical inter-relationship of these risk factors and further prediction of CVD events in an individual.

The most recent CVD risk prediction model based on vascular age in FHS cohort can be used for prediction of both general as well as risk of specific CVD events such as coronary artery disease, cerebro-vascular event etc.[4] Also the vascular/heart age determined by FHS methodology can be correlated with the chronological age for further comparison. The systematic review of cardiovascular risk assessment tools analyzed 102 risk models revealed that Framingham risk score model performed well in United States but have problems in absolute risk prediction, probably due to low/high baseline risk in the destination population.[5] The study also concluded that external validation of diabetes specific risk models is lacking. In this view the current study will highlight the utility of Framingham risk score (FRS) in Indian population and the concept of early vascular ageing especially applicable among diabetes will further strengthened the validation of FRS. CVD affect younger age-groups in South-East Asia Region than their counterparts in western countries.[6] CVD mortality in India in the 30–59 years age-group is twice than that in the US. Therefore this study has greater implications on prevention of early vascular aging and further CVD events.

To assess the rationale of the study following research gap analysis was performed.

1. Existing CV risk prediction models: several researchers developed various risk prediction models for CVD aiming at prevention and control of CVD for local and global applications. Further the CVD predictions were imported, validated, calibrated and tested in several external population.

Framingham risk scores noted to be among the most widely used tools. Framingham risk scores developed by Wilson et al and Anderson et al were the most commonly referred and validated CVD risk prediction tools in many countries.[7]

D'Agostino et al introduced vascular ageing based CVD risk prediction model in US population.[4] Though widely used, these CV risk prediction models have many limitations for external applicability outside United States (US) as follows:

i. *Transportability*: The author (D'Agostino et al) themselves agreed that the transportability of FRS need to be evaluated before use in other populations, due to diversity of baseline prevalence of risk factors, vulnerability to CV disease etc.[4]
ii. FRS noted to overestimate the risk in several individuals e.g. Selavarajah et al observed FRS overestimates CV risk for persons on anti-hypertensive medications and on lipid lowering therapy.[8]
iii. Brindle et al evaluated the application of FRS in diverse socio-economic population.[9] They observed that FRS underestimates CVD risk among socio-economically deprived individuals.
iv. WHO/ISH models provided visual chart based risk estimation tools stratified according to various geographical regions. These tools were reported to significantly underestimate the CV risk among several regions including some of the Asian countries such as Cambodia, Malaysia, Mongolia, Cuba and Jamaica.[8]
v. Conroy et al reported that QRISK scores developed using European Clinical attendance, used non-random sample and non-standardized methods for developing CVD risk prediction scores.[10]
vi. Reynolds risk scores were developed to use only among women.[11]
vii. In the PROCAM study, the participants were industrial employees therefore the applicability of risk scores among women was limited due to chance of underestimation.[12]
viii. It was reported that 15-20% of the MI patients have none of the traditional risk factors; therefore they were considered to have lower risk by the prediction scores.[13]
ix. Cuende et al reported SCORE scales. The limitation of these scores was that they evaluated end points as only fatal CV risk.[14] Therefore lacks in predicting non-fatal CV events.

2. Ethnic susceptibility of Indian population in US, Europe and other countries explored by Yusuf et al.[15]
3. Calibration and validation of existing risk prediction models were difficult to use in Indian settings due to lack of nationwide reliable estimates of epidemiological and risk factor data.[7]
4. Non laboratory based methods were compared for prediction of CV risk with laboratory methods by Gaziano et al for use in limited resource settings, noted to provide reliable estimates only for fatal CV events.[16]

5. Due to lack of indigenously developed CV risk prediction models among Indian populations restricts accurate estimation of CVD risk among Indians.
6. Several CVD risk prediction models were validated in Indian population.
   a) Chow calibrated FRS among Indians; he concluded that the calibrated FRS may fail to address accurate risk estimation among all the regions of India and reiterated the importance of locally developed CV risk prediction model.[17]
   b) Guha et al reported that FRS predictions among Indians fail to identify CV risk among non-diabetic patients.[18]
   c) Risk stratification based aggregate risk factor burden, as reported by Jeemon et al can be applied in Indian settings but lack validation and calibration (Figure 1).[19]

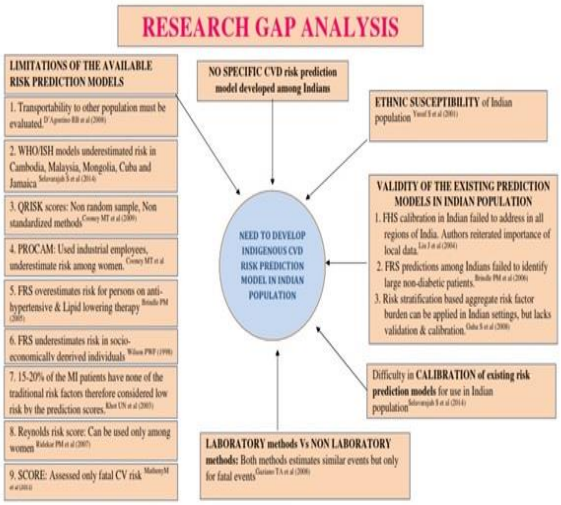

Figure 1: Research gap analysis.

Objectives

The objectives of the research study will be as follows:

1. To determine vascular age of the study participants using Framingham risk prediction model.
2. To assess the relationship of vascular ageing and risk of development of cardiovascular disease among the study participants.
3. To compare predictive accuracy of Framingham risk prediction model in predicting CV event.

METHODS

Study design and settings

The current cohort study will be conducted at the field practice area of Urban and Rural Health Training Center of Tertiary care institution in Central India, The field practice area of the present tertiary care teaching hospital comprise of an urban agglomeration catered by Urban Health Training Centre and a rural extension training and service arm Rural Health Training Centre comprising of approximately 30, 000 population each.

Study duration

The study will be conducted in four years, out of which the study subjects will be followed up for the period of three years during the study period.

Sample size estimation

The sampling cohort will be consisted of adult men and women residing in the field practice area during the study period. The primary study objective is to determine risk of cardiovascular disease among the individuals having risk factors but not the disease (CVD). To fulfill the objective the sample size was estimated to bear adequate representation of risk factors under study. Therefore the sample size was calculated based on the range of sex wise prevalence of risk factors available, in the Indian context. The lowest prevalent risk factor among both sexes was evaluated and the sample size was calculated accordingly. Based on the observations of multi-centric study by Indian Council of Medical Research in 2012, among the major risk factors of cardiovascular disease, diabetes was noted to be the least prevalent, that is 3% among men and 2% among women. While the expected proportion of cardiovascular disease among persons without diabetes and other risk factors was noted to be 0.01 among men and 0.0025 among women. With 95% confidence level, 80% power and 50% relative precision; using World Health Organization Sample size determination tables[20] the sample size was calculated as 566 males and 366 females. Therefore considering 10% attrition 2050 participants will be recruited from urban (n=1025) and rural (n=1025) field practice area.

Recruitment of participants

Inclusion criteria

A. Inclusion criteria for persons without risk factors

1. Adults in the age group of 31 to 60 years at the time of enrolment.
2. Resident of field practice area of the tertiary care Institution in Central India who were likely to stay at least for the period of three years for follow up.
3. Willing to provide written consent for participation into the study.

B. Inclusion criteria for persons with risk factors

In addition to above following additional inclusion criteria was applied for persons with risk factors.

1. Persons with known risk factors showing no evidence of cardiovascular disease.

Exclusion criteria

A. Exclusion criteria for persons without risk factors:

1. No past history of cardiovascular events (namely Coronary heart disease (CHD), Stroke etc.) at the time of enrolment or no evidence of past cardiovascular event as assessed by 12 leaded ECG and other investigations as requested by the physician for further ascertainment.

B. Exclusion criteria for persons with risk factors

In addition to above, individuals with following conditions were excluded from the study

1. Individuals with known risk factors on evaluation shown evidence of cardiovascular disease.

Ethical considerations

An informed consent document was developed and approved by the ethics committee of the tertiary care teaching institution; this consent format will be signed by all the participants before entry into the study as well as by the interviewer. The participants will be made aware that they can withdraw their participation at any time during the study freely without stating any reason. Only aggregated data will be reported in the publications without revealing any personal identity of any of the participant.

Data collection and sampling technique

The sampling technique and data collection procedure will be as follows:

i. *Piloting*: Pilot testing will be conducted to validate the data collection instrument and to enlist the community characteristics such as number of families, number of individuals in 31-60 years of age through a community based survey. The unit of selection will be an individual between 31-60 years age.

ii. *Sampling technique*: As per the routine health survey by Department of Community Medicine in the rural field practice area of RHTC and UHTC; approximately 2181 males and 1970 females in rural area and 3220 males and 2994 females urban area will be available for the study. Selection of the first individual will be by computer generated random number and subsequent individuals will be selected by adding sampling interval to the first selected number, similar technique will be followed for selection of study subjects from rural area. Further, 566 males and 366 females will be selected from urban (n=932) and rural area (n=932) each using stratified random sampling technique.

iii. *Data collection process*:

a. *Enrolment:* After obtaining due consent from the study participant, the participants will be enrolled into the study.
b. *Collection of baseline information:* After the enrolment the baseline information regarding socio-demographic and family profile, medical and personal history will be collected on predesigned and pre-tested questionnaire through face to face interview. Standard procedures for anthropometry and blood pressure measurement will be followed.[21-23]

Investigations

All the study participants will be subjected for blood glucose and cholesterol estimation investigations at Hospital of the tertiary care institute using using Randox - Imola Random auto-analyzer. All the participants will be analyzed on this analyzer and none be tested on any of the other equipment. Recommendations of eighth report of the Joint National Committee on hypertension will be followed for the diagnosis of hypertension. Recommendations of joint committee of International Diabetes Federation will be followed for diagnosis of diabetes.[23,24]

If the participant found to be having any of the known risk factor for CVD, the individual will be managed accordingly. A baseline electrocardiogram will be performed to ascertain old myocardial event; if any noted, then he/she will be excluded from the study. Individuals with existing risk factors will be counseled to reduce further risk of CVD. Also clinical evaluation of CV risk will be performed in accordance with WHO guidelines.[25] Vascular age will be determined using Framingham Risk Scales.[4]

Risk communication

After enrolment all the individuals were subjected for detailed clinical and anthropometric evaluation. Investigations for blood glucose and blood cholesterol estimation will be done and the results will be entered in the MS excel programme. This e-data base will be utilized for calculation of baseline risk of each individual. The participants' baseline risk of cardiovascular disease will be assessed. Individuals having higher baseline risk will be communicated for further counseling and medical attention as the routine screening protocol.

The study subjects showing no evidence of CV events enrolled into the study and followed up for the period of three years from the baseline for development of any of the cardiovascular disease. They will be communicated and ascertained about occurrence of any symptoms of the CVD at the baseline and during the follow up period. The individuals already diagnosed to have CVD will be excluded, other individuals with history suggestive of

CVD or impending CVD will be further investigated at the study site.

Assessment of the outcome (end points)

The individuals enrolled into the study will be followed up for occurrence of any of the cardiovascular event as follows.

- *Coronary artery disease*: The coronary artery disease will be recorded for Coronary death, Myocardial infarction, Coronary insufficiency or Angina.
- *Cerebro-vascular disease*: Ischemic stroke, Hemorrhagic stroke and Transient ischemic attack will be evaluated.
- *Peripheral arterial disease*: Intermittent claudication and heart failure will be assessed.

Each participant will be followed over the period of three years and they will be asked for history of cardiovascular events (if any). Participants reporting ailments suggestive of cardiovascular events will be further evaluated, noted and managed accordingly. The ascertainment of CV events will be performed by the cardiologist using electro-cardiographic, echo-cardiographic or enzymatic methods in each of the individual. The risk of individual CV will be calculated; an epidemiological model will be developed for predicting 10 year risk of CVD among individuals having risk factors but not witnessed any CVD event. The estimated risk prediction model will be compared with the existing Framingham risk scores and WHO/ISH risk prediction charts.[25] The utility of these risk prediction models among Indian settings will be evaluated and found suitable the model developed by the current research project will be recommended for prediction of risk among the individuals who have risk factors but not yet developed clinically manifest CV event (Figure 2).

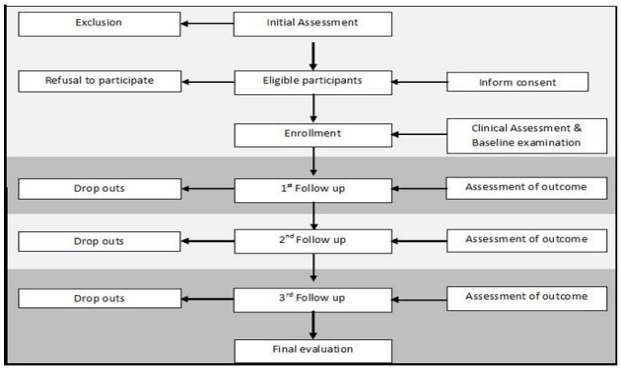

Figure 2: Subject enrollment and follow up flow chart.

Data analysis

The collected data will be entered into MS excel and further analyzed using SPSS ver. 16. The collected data will be analyzed with proportions; tests of significance will be applied wherever necessary. Descriptive data will be depicted in the form of proportions percentages, graphs, tables etc. Analytical statistics will be performed using various tests of significance like chi square test, t test etc. in univariate and multivariate analysis. The significance level will be considered at $p<0.05$ level. SPSS 16.0 was used to generate statistical model and regression equations. Logistic regression model using backward LR method will be used to identify significant risk factors of CVD. Linear regression will be used to determine the independent association of the risk factors for vascular ageing.

Limitations of the study

1. Silent event: Silent events which may occur among patients with neuropathy such as in diabetic neuropathy may have silent myocardial infarction which may not be noticed by the patients. As the study did not carry out active surveillance of the individuals during follow up these silent events may be missed by the study. The bias will be minimized by examination of persons with known history of diabetes with ECG.

2. As the study will not compel its study population to consult a specific health facility, the study subjects may consult varied health facilities, which may lead to classification bias as the practice of diagnosis of cardiovascular events may not be uniform at all levels. This bias will be minimized by inclusion of events diagnosed only by either of standard ECG changes, enzymatic changes, and angiographic methods.

Therefore the current population based prospective cohort study (probably the first in India) will be carried out to estimate cardiovascular risk among young individuals who have not developed clinically manifest cardiovascular events using the Framingham risk assessment model. The Framingham risk prediction model which was one of the most widely used for prediction of cardiovascular risk in many countries; will be assessed for accuracy in prediction of cardiovascular event among Indian population. Based on three years follow up of the study cohort, the risk factors for incident cardiovascular events will be assessed. According to the observed CV events over the period of three years a cardiovascular risk prediction model will be developed and validated to use in Indian population. The predictive accuracy of the newly developed risk prediction model will also be tested against the Framingham risk prediction model.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Dantas AP, Jimenez-Altayo F, Vila E. Vascular aging: facts and factors. Front Physiol. 2012;3:325.
2. Nilsson PM, Nilsson J-Ao, Berglund G. Population-attributable risk of coronary heart disease risk factors during long-term follow-up: the Malmo Preventive Project. J Internal Med. 2006;260:134–41.
3. Jani B, Rajkumar C. Aging & vascular aging. Postgrad Med J. 2006;82:357–62.
4. D'Agostino RB, Vasan R, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study, Circulation. 2008;117:743-53.
5. Matheny M, McPheeters ML, Glasser A, Mercaldo N, Weaver RB, Jerome RN, et al. Systematic Review of Cardiovascular Disease Risk Assessment Tools. Evidence Synthesis No. 85. AHRQ Publication No. 11-05155-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
6. Vani K. Non-communicable diseases in South-East Asia Region-2011; Situation and response. World Health Organization, New Delhi, 2011.
7. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-47.
8. Selavarajah S, Kaur G, Haniff J, Cheng KC, Hiong TG Graaf Yvd, Bots ML. Comparison of Framingham Risk Score, SCORE and WHO/ISH cardiovascular risk prediction models in an Asian population. Int J Cardiol. 2014;176(1):211-8.
9. Brindle PM, McConnachie A, Upton MN, Hart CL, Smith GD, Watt GCM. The accuracy of the Framingham risk-score in different socioeconomic groups:a prospective study. British J General Pract. 2005;55:838-45.
10. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal CVD in Europe: SCORE project. Eur Heart J. 2003;24,987–1003.
11. Ridker PM, Buring JE, Rifai N, Cook NR, Development of CV risk algorithm in women, the Reynolds Risk Score. JAMA. 2007;297(6):611-9.
12. Assmann G, Cullan P, Schulte H. Simple Scoring Scheme for Calculating the Risk of Acute Coronary Events Based on the 10-Year Follow-Up of the Prospective Cardiovascular Münster (PROCAM) Study. Circulation. 2002:105:310-5.
13. Khot UN, Khot MB, Bajzer CT, Snapp SK, Ohman EM, Brener SJ. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA. 2003;290:898-904.
14. Cuende JI, Cuende N, Lagartos JC. How to calculate vascular age with the SCORE project scales:a new method of cardiovascular risk evaluation. Eur Heart J. 2010;31:2351–8.
15. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases, Part II: Variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation. 2001;104:2855-64.
16. Gaziano TA, Young CR, Fitzmaurice G, Atwood S, Gaziano JM. Laboratory based versus non-laboratory based methods for assessment of cardiovascular disease risk: the NHANES I Follow-up study cohort. Lancet. 2008;371(9616):923-31.
17. Chow CK, Joshi R, Celermajer DS, et al. Recalibration of Framingham risk equation for a rural population in India. J Epidemiol Community Health. 2009;63:379-85.
18. Guha S, Pal SK, Chattarjee N, Guha S, Ghosh A Deb PK. How predictive is the Framingham's risk prediction algorithm in Indian perspective? A retrospective case-control study from Kolkata. Indian Heart J. 2008;60:330-2.
19. Jeemon P, Prabhakaran D, Huffman MD, Ramakrishnan L, Goenka S, Thankappan KR. Distribution of 10 year and lifetime predicted risk for cardiovascular disease in the Indian sentinel surveillance study population (Cross-sectional survey results). BMJ Open. 2011;1:e000068.
20. Lwanga SK, Lemeshow S. Sample size determination in health studies:A Practical Manual: World Health Organization, Geneva:1991.
21. National Health and Nutrition Examination Survey. Anthropometry Procedures Manual. CDC, Jan. 2007.
22. National Health and Nutritional Examination Survey III Cycle 2. Pulse and blood pressure procedures for household interviewers. 1989; Westat, Inc. 1650 Research Boulevard, Rockville, MD, 20850.
23. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guidelines for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(17):1809.
24. Colaguiri S, Aschner A, Beck-Nielsen H, Bennett P, Boulton, Colagiuri R, et al. Global Guidelines for Type 2 Diabetes. (2012) Clinical Guidelines Task Force, Int Diabetes Federation, Brussels, Belgium.
25. Romdhane HB, Damasceno A, Ebrahim S, Escobar C, Gueyffier F, Jackson R, et. al. Prevention of cardiovascular disease: Guidelines for assessment and management of total cardiovascular risk., WHO Press, World Health organization, 20 Avenue Apia, 1211 Geneva, 2007.

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