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RESEARCH ARTICLE

COMPARISON OF FRAMINGHAM RISK SCORE AND GLOBORISK AMONG TYPE 2 DIABETES SUBJECTS WITH AND WITHOUT CVD

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ABSTRACT

Objective: Cardiovascular risk prediction models are very effective way to assess the 10 years cardiovascular disease risk prediction among the populations. The present study determined the validity and utility of two important risk prediction models Framingham Risk Score (FRS) and Globorisk among Type 2 Diabetes (T2DM) subjects with cardiovascular disease (CVD) and without CVD. ***Methods:*** **C**onsecutively 208 subjects with T2DM were recruited and they were categorized into 2 groups: Group 1 consisted of 103 patients with CVD and Group 2 consisted of 105 patients without CVD. 10-years CVD risk estimations for both groups were assessed using two risk calculators. FRS and Globorisk. Risk equation, Sensitivity and Specificity were examined by comparing areas under the receiver operating characteristic (ROC) curve to evaluate the discriminative ability of competing risk model. ***Results*****:** Out of 208 study subjects analyzed for CVD risk by 2 models. FRS CVD risk assessment was better compared with globorisk, where FRS showed nearly 56.3% of high risk individuals with a statistically significance (p=<0.0001) when compared between CVD and Non-CVD subjects. ***Conclusion***: Framingham risk score showed better performance than globorisk score. FRS model can be better tool than globorisk in predicting the high cardiovascular risk subjects with T2DM.

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INTRODUCTION

Cardiovascular Disease (CVD) and diabetes are two major leading cause of early mortality among Indian population, about 65 percent of people with diabetes die due to heart disease and stroke. CVD showed a drastic increase among the Indian population (Chauhan *et al.,* 2013) which have outgrown the barriers of gender, locale, and economic status. Patients with Type 2 diabetes (T2DM) have a 4-fold increased risk for cardiovascular disease (CVD) and associated clinical complications (Zhao *et al.,* 2017) like high blood pressure, elevated lipid profile, physical inactivity, addiction and some non modifiable risk factors like age, sex and family history which contribute to increased incidence of CVD (Malik *et al.,* 2015). The cardiovascular risk prediction models are non-invasive approach in prevention and management of CVD and also in identification of high-risk individuals, the two major globally accepted risk prediction equations are Framingham Risk Score (FRS) and globorisk, and this equations have been developed and validated to estimate cardiovascular risk. The prediction scores are practical, easy to use tools at the level of

The assessment of CVD risk factors has been a key element to define a working predictive model for CVD (Borhanuddin *et al.,* 2018). Different guidelines recommend different risk score calculators to assess the 10-year cardiovascular risk and their management, depending on their risk scores (Garg *et al.,* 2017) and often represented as risk charts (Ueda *et al.,* 2017). The best known and probably the most widely used globally is the Framingham Risk Score (FRS). The FRS is the first equation for risk prediction, which was adopted by the Adult Treatment Panel III and has been widely, used worldwide (Cho, 2018). It is a simplified and common tool for the assessment of risk level of CVD over 10 years. It has been stated that subjects with T2DM without a previous history of CVD have the same risk of CVD as non-diabetic subjects with a history of CVD which has led the National Cholesterol Education Program to consider diabetes as a coronary heart disease risk equivalent (Matheus *et al.,* 2013). The Indian population who develop CVD at an early age and high rate are considered at risk (Garg *et al.,* 2017). Globorisk is an important advancement in the field of global cardiovascular risk prediction. It can be calculated in two modes, laboratory-based and office-based.

For diabetes subj ects, laboratory-based calculator is used considering the clinical data. CVD risk estimates may serve not only as a basis for preventive treatment, but also as a useful approach for risk communication with the affected individuals (Borhanuddin *et al.,* 2018). Hence, the objectives of this study was to assess the Specificity of Framingham Risk Score (FRS) and Globorisk score in predicting the 10-year CV risk using risk scoring tools among established CVD and Non-CVD subjects with Diabetes mellitus.

MATERIALS AND METHODS

Study population: The data of 208 subjects with Type 2 diabetes, who were admitted at a Tertiary care center for diabetes in Chennai, South India, between February 2018 to July 2018 was recorded for this study. The subjects were classified into 2 groups as CVD and Non-CVD based on the clinical examination and history of myocardial infarction. The diagnosis of MI was based on 3rd universal definition of MI (Kristian *et al.,* 2012). Group 1 consisted of 103 CVD subjects who were under treatment, 75.7% Men and 24.2% Women. Group 2 consisted of 105 Non-CVD subjects, 68.5% Men and 31.42% Women. Subjects with T1DM, Gestational diabetes, and patients with HIV and cancer were excluded from the study. Clinical data of the subjects including history and anthropometric parameter of subjects was collected from the hospital electronic database. Height and body weight were measured and Body Mass Index (BMI) was calculated. Subjects were classified as active smoker if they had smoked in the previous 12 weeks. Smoking or tobacco use in any form during the preceding month was also considered to be a CV risk factor. Blood pressure was measured using a standard sphygmomanometer. Routine biochemical investigations values such as Fasting Blood Sugar, Post Prandial blood sugar, HbA1c and lipid profile were noted. 10-year CVD risk estimation for both groups was done using two risk calculators FRS and Globorisk. These risk scores were compared in diabetic subjects with established CVD and Non- CVD.

Cardiovascular risk stratification: Cardiovascular risk was stratified into three categories; low, intermediate, and high risk based on the calculators used in this study (Nery *et al.,* 2013). High cardiovascular risk was defined as ten-year risk of ≥ 20 % and ≥30% for FRS and globorisk respectively. Low risk of ≤10 % was used in both FRS and globorisk. All other values were considered as intermediate risk group. The link to the online calculators used to predict the cardiovascular risk score are https://www.framinghamheartstudy.org/ and http://www.globorisk.org/.

Framingham risk score: The Framingham risk score is a multivariable and gender specific risk function that predicts 10-year risk of developing CVD (coronary heart disease, stroke, peripheral artery disease or heart failure). The clinical parameters included (FRS-CVD) in calculations are age, gender, total cholesterol and high-density lipoprotein, systolic blood pressure, treatment for hypertension, smoking, and diabetic status. Table 1 represents the characteristics of the variables included in this model.

Globorisk score: Globorisk is a global risk predictor for cardiovascular disease which predicts risk of heart attack or stroke in healthy individuals for all countries in the world. It uses the information on a person's country of residence, age, gender, smoking status, systolic blood pressure, diabetes, and total cholesterol to predict the individual risk of heart attack or stroke in next 10 years. It can be calculated in two modes, laboratory-based and Office-based. If the person does not have any recent diabetes or cholesterol test, they can use the office-based version of Globorisk which is based on body weight and height instead. In the present study we used laboratory based version as we have included known diabetes cases with clinical data. Table 1 represents the characteristics of the variables included in this model.

Model performance: To evaluate the performance of prediction models, discrimination and calibration are the 2 essential aspects. Sensitivity and specificity were examined by comparing areas under the Receiver-Operating Characteristic (ROC) curve to evaluate the discriminative ability of this competing risk model. Comparisons of models were statistically tested for the differences in the area under the ROC (AUC).

Statistical method: Data were represented as Mean ± Standard deviation. Chi-square test was used for categorical variables to determine if the observed 10-year cardiovascular mortality rates differed significantly from the expected. A p value <0.05 was considered statistically significant. Analysis were performed using IBM SPSS Statistics for windows, version 25.0 (IBM corp armonk, NY, USA) and stata statistical software: Release 11.0 (college station, TX: stata corporation)

RESULTS

Baseline characteristics: A total of 208 T2DM subjects aged between 30 and 75 were recruited for the study. Table 2 shows the correlation between clinical parameters based on gender. 72% of the overall population was men and 28% were women; cardiovascular risk factors were more prevalent in women than men. Women shows a higher BMI (P=0.005), Total cholesterol (P=0.001), and HDL levels (P=0.016). When the study population was divided based on their CVD events, it was found that a significant difference was seen among the groups in parameters such as Systolic blood pressure (p= 0.010), Duration of diabetes (p=<0.0001) and Total cholesterol (p= 0.052) and nearly 83% of the subjects were having high blood pressure which was shown in Table 3. The subjects with elevated clinical features were underwent stating treatment, hence the value shows lesser and non-significant.

Cardiovascular risk stratification and distribution: The assessment of cardiovascular risk by FRS and Globorisk are shown in Table 4 and Table 5 respectively. The 10-year CV risk estimates derived using the two risk scores showed progressive cardiovascular risk prediction. Table 4 represents the risk estimation based on the presence or absence of CVD events. When the risk stratification was done among groups, in FRS, we found high risk among CVD group which was nearly 56.3% and a highly significant p-value of <0.0001. Low cardiovascular risk score with a percentage of 33.3% was found significant among Group 2. Globorisk predicted only low risk in Group 2 with a p-value of 0.008, and no significance was found among moderate and high categories. Tables 5 represents the gender based differentiation among the 2 risk calculators, and have found 64.1% men have high risk score and 32% of women subject in Group1 using FRS. And a strong evidence of women at a lower risk was strongly predicted using FRS. When estimated using Globorisk, no significance was observed among all the risk scores.

Table 1. Characteristics of Framingham risk score and Globorisk prediction models

	Characteristics of models	
	Framingham Risk score	**Globorisk score**
Variables included in the the models	Age (35-75)	Age (35-69)
	Gender	Gender
	Total cholesterol	Total cholesterol
	HDL cholesterol	--
	Systolic blood pressure	Systolic blood pressure
	Smoking status	Smoking status
	Diabetes status	Diabetes status
	Hypertensive treatment.	--

Table 2. Clinical and anthropometric parameters based on gender

Variables	Men (n=103)	Women (n=105)	p-value
Age (in years)	55.97 ± 9.955	52.86 ± 9.193	0.041
Body mass index (kg/m^2)	27.35 ± 4.470	29.42 ± 5.579	0.005
Systolic blood pressure (mm Hg)	127.18±16.642	129.48±17.906	0.382
Diastolic blood pressure (mm Hg)	77.05±8.689	77.31±8.398	0.843
Duration of diabetes	14.789±9.167	10.703±6.663	0.002
Family history of Diabetes	67.4%	32.6%	0.027
Previous history of cardiovascular disease	52.0%	43.1%	0.250
Smoking	14.0%	--	
Hypertension	68.7%	70.7%	0.777
HbA1C (%)	8.981 ± 2.0299	9.160 ± 2.0028	0.568
Total cholesterol (mg/dL)	142.29 ± 41.362	163.69 ± 42.205	0.001
HDL (mg/dL)	37.15 ±13.334	41.74 ± 8.833	0.016
LDL (mg/dL)	80.71±28.574	87.64±27.369	0.114

*Data are % for categorical variables and mean (SD) for continuous variables. Abbreviations: HDL= High density lipoprotein, LDL= Low density lipoprotein.

Table 3. Clinical and anthropometric parameters based on study subjects

Variables	Group-1 (CVD) (n=103)	Group-2 (Non-CVD) (n=105)	p-value
Age (in years)	58.57±8.931	51.70±9.503	<0.0001
Body mass index (kg/m^2)	28.10±4.96	27.67±4.81	0.0451
Systolic blood pressure (mm Hg)	130.88±17.325	124.82±16.183	0.010
Diastolic blood pressure (mm Hg)	76.95±8.608	77.29±8.609	0.780
Duration of diabetes	16.5550±9.483	10.8013±6.833	<0.0001
Family history of Diabetes	71.8%	63.8%	0.237
Previous history of cardiovascular disease	100%	---	
Smoking	7.7%	12.3%	0.358
Hypertension	82.5%	56.2%	<0.0001
HbA1C (%)	9.092±1.9875	8.972±2.0570	0.671
Total cholesterol (mg/dL)	142.48±38.458	153.92±45.776	0.052
HDL (mg/dL)	38.29±9.031	38.57±15.031	0.871
LDL (mg/dL)	79.61±26.660	85.61±29.742	0.127

*Data are % for categorical variables and mean (SD) for continuous variables. Abbreviations: HDL= High density lipoprotein, LDL= Low density lipoprotein, CVD= cardiovascular disease.

Table 4. Risk estimation based on the FRS and Globorisk among subjects

10- year CV risk	Framingham Risk score			Globorisk score		
	Group-1 (CVD)	Group-2 (Non-CVD)	p-Value*	Group-1 (CVD)	Group-2 (Non-CVD)	p-Value*
Low risk	10.7	33.3	<0.0001	0	6.7	0.008
Moderate risk	33	37.1	0.532	79.6	76.2	0.552
High risk	56.3	29.5	<0.0001	20.4	17.1	0.549

Table 5. Gender based comparison of 10-year cardiovascular risk among study subjects

10- year CV risk		Framingham Risk score		Globorisk score			
		Men	Women	p-Value*	Men	Women	p-Value*
1*	Low risk	3.8	32.0	<0.0001	0	0	---
	Moderate risk	32.1	36.1	0.715	82.1	72.0	0.278
	High risk	64.1	32.0	0.005	17.9	28.0	0.278
2*	Low risk	25.0	51.5	0.007	4.2	12.1	0.129
	Moderate risk	36.1	39.4	0.747	77.8	72.7	0.573
	High risk	38.9	9.1	0.002	18.1	15.2	0.714

*1 - Group-1 subjects with CVD; *2- Group-2 subjects with Non-CVD; Values are given in percentage (%)

Table 6. Sensitivity, specificity and discriminative ability for the FRS and Globorisk models for 10- year cardiovascular risk

Models	Cut-off	Sensitivity	Specificity	AUC (95% CI)
FRS				
Overall	> 20	56	70	0.654 (0.490,0.843)
Men	> 20	64	61	0.615 (0.398, 0.833)
Women	>20	32	91	0.800 (0.509,1.000)
Globorisk				
Overall	> 30	20	83	0.594 (0.316,0.684)
Men	> 30	17	81	0.500 (0.278,0.722)
Women	> 30	72	85	0.500 (0.155,0.845)

Values are in percentage (%); AUC, area under the receiver operating characteristic curve

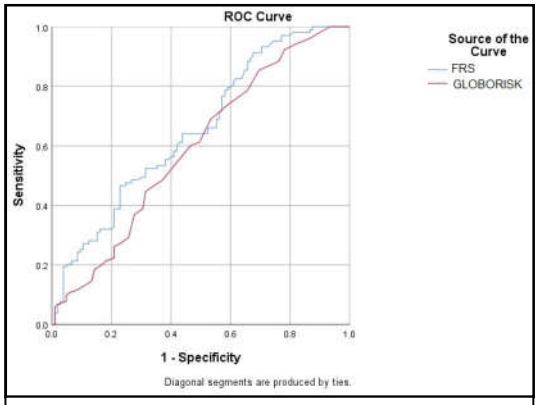

Figure 1. ROC curves for the FRS and Globorisk models for prediction of cardiovascular risk in overall study group.

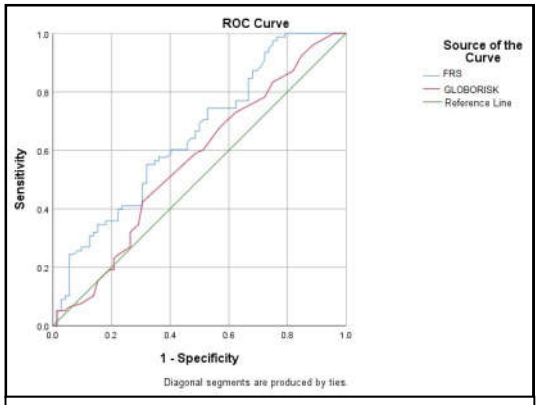

Figure 2. ROC curves for the FRS and Globorisk models for prediction of cardiovascular in men

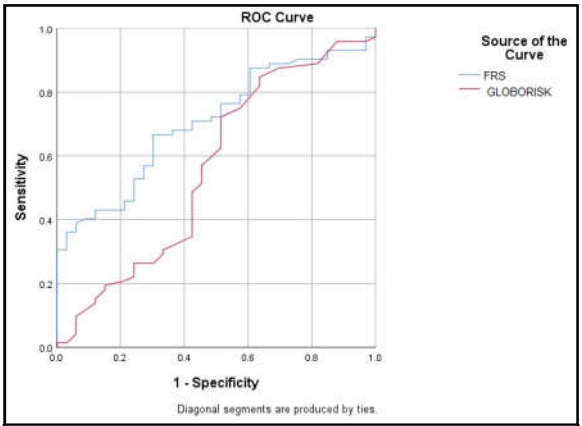

Figure 3. ROC curves for the FRS and Globorisk models for prediction of cardiovascular in women

Assessment of risk stratification models: We calculated the sensitivity and specificity among the two scoring model by comparing the areas under the receiver-operating characteristic (ROC) curve. When the whole study population was analysed, Framingham model were found to be effective in predicting the presence of cardiovascular disease Table 6. The area under the ROC curve analysis for CVD and Non- CVD revealed slightly higher discriminative capacity for the Framingham (AUC = 0.654) than Globorisk (AUC =0.594). Figure 1 shows the graphical representation of the ROC curves to compare the prediction rate among FRS and Globorisk in overall study population. The area under the ROC curve analysis showed better discrimination for the FRS than globorisk. Figure 2 indicate the ROC curves for the men population, where as Figure 3 showed the ROC curves discrimination among the women population of the study population. When men and the women were evaluated using FRS, women had higher discrimination (AUC=0.800) than men, whereas in Globorisk, both shows same discrimination with poor performance. This study report emphasizes that the FRS can estimate CVD risk in type 2 diabetes subjects better than Globorisk.

DISCUSSION

This study is a cross-sectional analysis comparing two different CV risk calculators. Our study results demonstrated that the FRS stratification models were better in predicting both the presence and severity of CVD. Comparative studies on the relative performance often suggest that one model may be better than another. In particular, the FRS usually had superior performance compared with other models (Siontis *et al.,* 2012).

Our study also showed high percentage of high risk individuals, when compared with Globorisk. Many studies have coated the same results. Versteylen MO showed that in a stable chest pain population, the ability of FRS to predict for CVD was better compared to other models studied in their study. They also showed significance in low risk group using FRS (Versteylen *et al.,* 2011) which was also evident in our study. Another study by George CM siontis also found out FRS version was one of the best models compared and claimed to be superior (Nery *et al.,* 2013). Wannamethee compared the risk among the metabolic syndrome, and FRS and stated that the presence of the metabolic syndrome was found to be a significant predictor of CVD, but it was not as good as the FRS (Wannamethee *et al.,* 2005). Assessed CVD risk perception asking about the risk of developing a heart attack within 10 years and stated that, for identification of high CVD risk group in Indians, FRS CVD risk assessment model is most useful (Garg *et al.,* 2017).

Contrary to the positive results of FRS some studies even showed FRS as bad predictor, for example a study by Lauro Ferreira compared FRS and the American College of Cardiology/American Heart Association (ACC/AHA) risk score in an HIV subjects, He found out that 61.3% were stratified as low risk by FRS, compared with 54% by ACC/ AHA score. Only 26.1% were classified as cardiovascular high risk by FRS whereas 46% by ACC/AHA score (Neto *et al.,* 2017). Weijden highlighted that men and participants with diabetes were more likely to perceive their CVD risk inappropriately (Weijden *et al.,* 2007); finally our study has shown a concordance with the above mentioned studies which also suggest FRS as a better predictor. Globorisk although have

few research evidences. To our knowledge, our study will be the first to describe about this risk score in Indian population. Globorisk could not show any significance in risk prediction of CVD in our study, which was same in a study by Hendriks, he observed 10-year mortality risk using the Globorisk in subjects without cardiovascular diseases, he found out that predicted mortality risk decreased over time in both sexes and no evident of low risk score in women was seen compared to men (Hendriks *et al.,* 2015). Globorisk calculator for cardiovascular risk scores was analysed by Ueda P, in subjects with and without CVD, using laboratory-based measurements for 182 countries to predict 10-year risk of fatal and non-fatal CVD in adults. He found that risk factor profile was generally lower in High income countries than in low income countries. Central and Southeast Asia and Eastern Europe countries, including China and Russia showed highest risks. The proportion of people aged 40–64 years at high risk of CVD ranged from 1% for South Korean women to 42% for Czech men, and 2% in Uganda (men and women) to 13% in Iranian men. More than 80% of adults were similarly classified as low or high risk by the laboratory-based and office-based risk scores. The office-based model substantially underestimated the risk among patients with diabetes (Ueda *et al.,* 2017). Hence, Laboratory-based measurements were used in our study for the risk prediction.

The FRS model showed good discrimination for both Men and Women in our study, at the cut-off of 20% in FRS and 30% in Globorisk. The ability of FRS model to accurately stratify the risk has been proven in other studies (Selvarajah *et al.,* 2014). In Australian study, FRS had an AUC of 0.73 (95%Cl 0.69, 0.77) for men and 0.76 (95%Cl 0.72, 0.80) for women [(19)]. In Tehran study, AUC for men was 0.77 (0.74, 0.81) and women 0.82 (95%Cl 0.79, 0.85) (Bozorgmanesh *et al.,* 2011), which is similar to that was found in our study. Poor discrimination was seen in the Globorisk model with low AUC of 0.50 in both genders. Cardiovascular risk-prediction models in limited resource settings which play a very important role. The model cut-off point should be distinguished between the high and low-cardiovascular risk so as to optimize treatment for those who will benefit the most (Cook, 2008). For DM subjects with low-to-intermediate risk, preventive statin therapy may provide limited protective benefit while potentially influencing hypoglycemia.

Conclusion

Our study highlighted that it is important to assess subjects with diabetes for CVD risk using cardiovascular risk prediction models. These findings suggest that FRS model may be the most appropriate CV risk assessment algorithm to be used in Indians and applicable for use in clinical practice for the identification of subjects at high cardiovascular risk. In such subjects, risk assessment helps in considering statin initiation or intensification. This approach is only efficient when subjects understand and adhere to risk reduction therapy.

Conflict of interest: The authors have no conflict of interest to report.

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