ORIGINAL ARTICLE

The Role of Cardiovascular Risk Factors and Risk Scoring Systems in Predicting Coronary Atherosclerosis

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Abstract

Background: Comparative data on the performance of cardiovascular risk scoring systems (CRSSs) in patients with severe coronary artery disease (CAD) are lacking.

Objectives: To compare different CRSSs regarding their ability to discriminate patients with severe CAD.

Method: A total of 414 patients (297 men; 61.3±12.3 years of age) undergoing coronary angiography were enrolled and evaluated for major risk factors. Cardiovascular risk and risk category were defined for each patient using the Framingham, Systemic Coronary Risk Evaluation (SCORE), and Pooled Cohort Risk Assessment Equation (PCRAE) tools. Severe CAD was defined as ≥ 50% stenosis in at least one major coronary artery and/or previous coronary stenting or coronary artery bypass grafting. A $p < 0.05$ was considered statistically significant.

Results: Severe CAD was identified in 271 (65.4%) patients. The ROC curves of the 3 CRSSs for predicting severe CAD were compared and showed no significant difference: the area under the ROC curve was 0.727, 0.694, and 0.717 for the Framingham, SCORE, and PCRAE tools, respectively ($p > 0.05$). However, when individual patients were classified as having low, intermediate, or high cardiovascular risk, the rate of patients in the high-risk group was significantly different between the PCRAE, Framingham, and SCORE tools (73.4%, 27.5%, and 37.9%, respectively; $p < 0.001$).

Discussion: PCRAE had higher positive and negative predictive values for detecting severe CAD in high-risk patients than the Framingham and SCORE tools.

Conclusion: We can speculate that currently used CRSSs are not sufficient, and new scoring systems are needed. In addition, other risk factors, such as serum creatinine, should be considered in future CRSSs. (Int J Cardiovasc Sci. 2021; 34(1):32-38)

Keywords: Cardiovascular Diseases; Coronary Artery Diseases; Risk Factors; Atherosclerosis; Epidemiology; Coronary Angiography; Diabetes Mellitus; Hypertension; Renal Insufficiency; Heredity.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in developed countries.[1] According to the chronic disease report, there are about 2 million patients with CAD in Turkey[1]. About 17 million people all over the world and 200 000 living in Turkey are losing their lives because of cardiovascular diseases.[2]

Along with developing technology, a general rise in the consumption of high-fat and high-calorie foods and a decrease in physical activity have led to an increase in atherosclerosis and hypertension. Stroke and peripheral artery diseases, such as CAD, which are influenced by the same risk factors, also increase health care costs to a great extent and cause significant loss of labor force. Prevention and early detection of CAD have a substantial impact on

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the decrease of cardiovascular mortality, morbidity, and health expenditures.[3]

While the Framingham Heart Study has provided invaluable data on atherosclerosis and the natural history and epidemiology of CAD, modern medicine has introduced the concept of "risk factors" in cardiovascular disease. Risk factors can be described as parameters that predict future cardiovascular events. Potential coronary risk factors associated with biochemical-, genetic-, and lifestyle-related pathways have been well established with the understanding of the pathophysiology of atherosclerosis over the past 50 years, which has led to significant reductions in age-related cardiovascular mortality.[4]

The results of the Framingham Heart Study have served as a basis for other studies and have led to the development of new risk scales. In addition to the Framingham risk score (FRS), other risk probability models used to calculate total cardiovascular risk include the World Health Organization (WHO), Systemic Coronary Risk Evaluation (SCORE), Prospective Cardiovascular Münster (PROCAM), Joint British Societies 2 (JBS-2), QRISK, Scottish Intercollegiate Guidelines Network (SIGN), and Pooled Cohort Risk Assessment Equation (PCRAE) models. Many of these algorithms are based on age, sex, blood pressure, smoking, diabetes, and lipid levels. There are also relatively new scoring systems that focus on the number of additional risk factors, such as antihypertensive treatment, family history of coronary heart disease, social deprivation, high-sensitivity C-reactive protein (hs-CRP), and hemoglobin A1c (HbA1c) levels at a younger age.[5]

In all the different scoring systems that use the proposed quantitative risk assessment model to reduce the prevalence of cardiovascular disease in asymptomatic individuals, the most important aspect is that the low-risk population representing the largest group affected by the disease will not benefit from a high-risk strategy alone. In addition, risk models have disadvantages such as inability to quantitatively predict short-term absolute risk, inability to follow changes in the risk factor level or intensity (because the model focuses only on categorical risk factors), and the fact that the effect of advancing age is smaller than the progressive effect on absolute risk. Other problems that current risk scoring models need to overcome include the fact that they have not yet been adequately tested in clinical practice, they obscure the history of the risk factor (and therefore the changes in the risk factor level from one visit to the next), they focus on short-term rather than long-term risk assessment, and perhaps most importantly, whether they are adaptable to all populations remains uncertain.[6]

It is known that geographic region plays an important role in the distribution of risk factors. It is expected that risk factor distribution and density will be different according to geographic region. While PCRAE and FRS originated in North America, SCORE, PROCAM, the Reynolds risk score, and QRISK were developed mainly based on European societies. This reveals the need to test and compare the validity of risk models in different countries.

The present study aimed to determine and compare the ability of FRS and SCORE, risk assessment systems commonly used in practice, and especially of the relatively new PCRAE risk assessment system to detect high-risk patients in the Turkish population. It also aimed to determine the risk factors that may constitute a cardiovascular risk in these patients and that can be easily detected in routine examination by evaluating them one by one using logistic regression.

Methods

Study Patients

We conducted a prospective cross-sectional study of consecutive patients who underwent coronary angiography for the risk of coronary ischemia in 6 consecutive months in the year 2014 in the Department of Cardiology at the Gulhane Military Medical Academy, Ankara, Turkey. Eligible participants were all patients aged ≥ 18 years whose laboratory results were available from the hospital database. There were no exclusion criteria. In sample size calculation, we hypothesized that PCRAE would correctly predict 60% of the high-risk patients and, to detect a 15% difference with the FRS, we calculated that at least 364 patients needed to be included in the study, with a type I error of 0.05 and power of 80%. At the end of 6 consecutive months, we had enrolled 414 patients, which exceeded in approximately 10% the required sample size. Approval to conduct the study was obtained from the local ethics committee. Patients were informed about the study and individual consents were provided.

Preparation of the Database

For all patients, important medical history information was investigated, including age, sex, cardiac complaints, level of education, exercise frequency, nutritional

habits, smoking and alcohol consumption, coexistence of hypertension, hyperlipidemia, and diabetes mellitus, history of cardiac, neurologic, or other chronic disease, family history, and current medical treatment. Physical examination findings, such as blood pressure, height, and waist-to-thigh ratio, and laboratory findings, including complete blood count and available biochemical parameters, were evaluated in face-to-face preoperative visits for risk score analysis and other subgroup analyses. The FRS, SCORE, and PCRAE risk scoring systems were chosen for their popularity and conformity. Coronary angiograms were examined for disease extent and severity using the Gensini score. Patients who had coronary intervention or ≥ 50% stenosis were defined as having severe CAD.

Statistical Analysis

Continuous variables with normal distribution were expressed as means (SD). Normality of the data was examined by the Shapiro-Wilk test. Categorical variables were expressed as numbers and percentages. The sign test was used for paired comparisons of the mean risk levels calculated by the different risk scoring systems. The Friedman and sign tests were used to compare different risk scores. Stepwise multivariable logistic regression analysis with backward elimination was used to identify independent predictors of cardiovascular disease. C-statistics were used to compare receiver operating characteristic (ROC) curves. All variables with a $p < 0.05$ in the univariate analysis were included in the multivariable model. For each variable, the odds ratio (OR) and the corresponding 95% confidence interval (CI) were calculated. Each risk system had its variables weighted according to the regression coefficient. The discriminatory power of the risk model was assessed by calculating the area under the ROC curve (AUC). Cutoff values were defined as the highest values of the sum of sensitivity and specificity. Statistical analyses were performed using Medcalc and SPSS for Windows (version 20.0; SPSS, Inc, Chicago, IL). Statistical significance was set at $p < 0.05$.

Results

A total of 414 patients were included in the study. Of these, 297 (71.7%) were men and 117 (28.3%) were women, with a mean (SD) age of 61.3 (12.3) years. Demographic, clinical, and laboratory characteristics of the study population are shown in Table 1.

Table 1 - Demographic, clinical, and laboratory characteristics of the study population

PHYSICAL EXAMINATION	N = 414
Sex (female), n (%)	117 (28)
Age (years), mean ± SD	61.3 ± 12.3
Body mass index (kg/m^2), mean ± SD	28.2 ± 4.6
Systolic blood pressure (mm Hg), mean ± SD	130.5 ± 20.9
Diastolic blood pressure (mm Hg), mean ± SD	78.8 ± 12.5
Pulse pressure (mm Hg), mean ± SD	51.6 ± 15.3
COMORBIDITIES	
Hypertension, n (%)	241 (58.2)
Diabetes mellitus, n (%)	116 (28.0)
Smoker, n (%)	111 (26.8)
Chronic kidney disease, n (%)	66 (15.9)
Family history of coronary artery disease, n (%)	164 (39.6)
LABORATORY	
Hemoglobin (g/dL), mean ± SD	13.8 ± 1.9
Leukocyte (102/mm^3), mean ± SD	7.6 ± 2.8
Thrombocyte (102/mm^3), mean ± SD	243.70 ± 73.7
Fasting blood glucose (mg/dL), mean ± SD	124.8 ± 59.1
Urea (mg/dL), mean ± SD	36.3 ± 14.3
Creatinine (mg/dL), mean ± SD	1.0 ± 0.39
eGFR (mL/min) , mean ± SD	85.9 ± 27.6
Total cholesterol (mg/dL), mean ± SD	197.5 ± 44.6
LDL cholesterol (mg/dL), mean ± SD	123.4 ± 39.8
HDL cholesterol (mg/dL), mean ± SD	44.2 ± 10.6
Triglycerides (mg/dL), mean ± SD	166.6 ± 94.8
HbA1C (mg/dL), mean ± SD	7.3 ± 2.1

eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HbA1C: hemoglobin A1C.

The rate of patients with severe CAD was significantly high with all 3 risk scores used in the study. As expected, the Gensini score, which indicates prevalence in the group with severe vascular disease, was also high (Supplementary Table 1).

Patients were divided into low-risk, intermediate-risk, and high-risk groups according to the FRS, SCORE, and PCRAE scoring systems. Although the same population

was assessed by the 3 risk scoring systems, the distribution of risk groups was significantly different between them (Friedman test, X2 = 269.686, p < 0.001). When low-, intermediate-, and high-risk patients were scored as 1, 2, and 3 points, respectively, the mean risk category score of PCRAE was significantly higher than that of the other 2 systems (Supplementary Table 2). The rate of patients in the high-risk category was also significantly higher in the PCRAE system than in the other systems. Post hoc analysis showed a statistically significant difference in the binary comparisons between the 3 risk scoring systems (sign test, p < 0.001 for all comparisons).

There was no significant difference between the groups in AUC values (Supplementary Table 3) when comparing the power of ROC curves to determine the presence of severe vascular disease in subgroups considered to be at high risk according to the different risk scores.

After the patients were grouped according to risk category, as assessed by the 3 different risk models, the ROC curves were evaluated in relation to Gensini scores. The AUC values were 0.727, 0.717, and 0.694 for the FRS, PCRAE, and SCORE risk models, respectively (Supplementary Table 4), with a significant association of high Gensini score with severe coronary atherosclerosis.

A logistic regression test was performed to determine the effects of classical risk factors (age, sex, hypertension, diabetes, hyperlipidemia, and smoking) and renal insufficiency (estimated glomerular filtration rate [eGFR] < 60 mL/min) on predicting the likelihood of severe CAD ("likelihood"). The applied logistic regression model was found to be statistically significant (X2: 87.050, p < 0.001). The model described 27% of the severe CAD variance (Nagelkerke R2), with 73.8% of cases correctly classified (sensitivity of 89.0%, specificity of 44.1%, positive predictive value of 75.6%, and negative predictive value of 67.4%). The effects of the 5 variables included in the model (hypertension, hyperlipidemia, diabetes, male sex, and renal insufficiency) were statistically significant (Table 2).

Discussion

The primary goals of the present study were to assess the predictive value of risk factors in high-risk patients and to evaluate different risk scoring systems in terms of prediction of severe CAD. The cardiovascular risk category was higher in our sample compared with the general population as the study included only patients undergoing coronary angiography for suspected ischemia. Because risk factors differ according to geographic region, the effectiveness of risk scoring scales, mainly those developed in Europe and North America, is still uncertain. Therefore, the cardiovascular risk in the Turkish population remains a question to be answered.[7] Furthermore, the identification of the prevalence of potential risk factors may lead to the establishment of a cardiovascular risk score that reflects the overall risk in the Turkish population.

Initially, ROC curve and logistic regression analyses were used to determine the individual effects of risk factors such as age, sex, hypertension, diabetes, hyperlipidemia, chronic kidney disease, and smoking on coronary atherosclerosis. Creatinine and eGFR had the highest AUC values (0.648 and 0.647, respectively)

Table 2 - Logistic regression model for prediction of severe coronary artery disease

	B	SE	DF	P	OR	%95 CI
Hypertension	0.794	0.280	1	0.005	0.452	0.261-0.783
Sex	1.333	0.300	1	0.000	0.264	0.146-0.475
Hyperlipidemia	1.023	0.252	1	0.000	0.260	0.220-0.589
Diabetes mellitus	0.882	0.263	1	0.001	0.414	0.247-0.693
Smoking	0.394	0.281	1	0.164	0.674	0.389-1.168
Age	0.016	0.011	1	0.154	1.016	0.994-1.039
Renal Insufficiency	1.453	0.416	1	0.000	0.234	0.103-0.529
Coefficient	2.723	0.951	1	0.004	15.226	

B: Unstandardized beta; SE: Standard error; DF: Degrees of freedom; OR: Odds ratio; CI: Confidence interval (for OR)

among the parameters evaluated, with similar results obtained in the logistic regression analysis (OR: 0.234; p < 0.001). In the NHANES study, a close relationship was also observed between cardiovascular risk and renal dysfunction (eGFR < 60 mL/min/1.73 m^2): an eGFR reduction of 10 mL/min/1.73 m^2 in patients with eGFR < 60 mL/min/1.73 m^2 resulted in a 1.29 (95% CI, 1.06-1.55) increase in the risk of cardiovascular mortality[8-9] Although creatinine and eGFR are not included in the 3 risk models evaluated here (FRS, SCORE, and PCRAE), they were considered potential risk factors for predicting life-long cardiovascular risk. Subsequently, we evaluated and compared the data between the 3 different risk scoring systems under study. The rate of patients classified in each risk category (low, moderate, or high risk) was significantly different between the 3 systems (Friedman test, X2 = 269.686, p < 0.001).

The number of patients who fell into the high-risk category was significantly higher with the PCRAE tool (271/414 patients) than with the SCORE and FRS tools (121 and 87 of 414 patients, respectively). Also, the highest AUC value for the subgroups considered to be at high risk according to the different risk scores was obtained with the PCRAE risk model (0.673 vs 0.659 for FRS and 0.666 for SCORE). These findings seem to contradict the results of previous studies evaluating the PCRAE risk model. Maryam et al.[10], in a Rotterdam study of 4854 patients comparing the FRS, SCORE, and PCRAE tools, reported that SCORE provided the most appropriate risk model to categorize patient risk level, but all risk models predicted a higher risk than the current level. Additionally, the PCRAE risk model adopted in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines aimed at identifying individuals with higher actual risks to justify targeting them for statin treatment.[10] However, our sample consisted predominantly of high-risk patients, thus precluding a proper comparison of the results.

The association between risk score and CAD severity defined by the Gensini score was significant for all risk scoring systems evaluated. In addition, all scoring systems were able to significantly predict the presence of CAD, with only a slight difference between AUC values (FRS: 0.727, PCRAE: 0.717, and SCORE: 0.694). It should be noted that our study population is different from the original populations from which the models were derived. For example, age ranged from 20 to 85 years in the present study, an age range greater than that of the 3 risk models under study. Moreover, the models used hard clinical endpoints, whereas we used presence of CAD as an endpoint, and, most importantly, they included CAD-free patients, whereas we included only patients undergoing coronary angiography.

The value of newly defined risk factors has yet to be determined in these scoring systems, which usually have different combinations of the same classical risk factors. In general, patients are classified according to their risk factors for primary prevention. The FRS and SCORE scales have underestimated cardiovascular risk in terms of primary outcome, and the development of more accurate models has been desired. This is precisely why the PCRAE model, adopted in the 2013 ACC/AHA guidelines, has been put forward; however, it has also been criticized for overestimation and referral for unnecessary statin treatment, which was called "statinization".[11]

Because the aim of our study was to identify cardiovascular risk factors and to compare risk models for their ability to predict the presence and severity of coronary atherosclerosis, using conventional angiography as the gold standard is undoubtedly valuable. In the literature, the predictive value of risk models has been detected mostly by using coronary calcium scores and intravascular ultrasound (IVUS). The inclusion of the PCRAE risk model in the present study is also important as it supports the often criticized nature of this model, which greatly increases the use of statins compared to widely used conventional risk prediction models, such as FRS and SCORE.

Although studies evaluating the prediction of coronary atherosclerosis by risk scoring systems are limited,[12] coronary anatomy in these studies is mostly assessed by computed tomographic coronary calcium scanning to predict coronary atherosclerosis, and less frequently by IVUS and in small series of patients. Marso et al.,[13] in a multicenter study of 531 patients categorized by the FRS and evaluated by IVUS, showed an increase in plaque volume and thin-cap fibroatheroma in high-risk patients. Similarly, Takeshita et al.,[14] in 217 patients stratified by the FRS in whom coronary plaque volume was investigated by IVUS in non-stenotic left main coronary artery lesions, reported an association of increased atherosclerosis severity with increased cardiovascular risk. Rinehart et al.,[15] used computed tomographic coronary calcium scanning in 375 coronary segments and showed early vessel wall thickening in patients with intermediate to high risk according to the FRS. Ellis et al.[16], in a study of 1000 patients, reported high false positive rates for coronary calcium score assessment in individuals classified as low risk by the FRS, thus

suggesting calcium scoring as a complementary approach to standard risk identification strategies. In the present study (n=414), patients were grouped according to risk category, as assessed by the 3 different risk models, and the Gensini scores were then calculated according to the results of coronary angiography to determine the severity of coronary atherosclerosis in an attempt to determine the correlation between them. This study design had been previously used only by Sayin et al.,[17] and we adapted it to a larger patient population to evaluate risk categorization of patients using SCORE and PCRAE in addition to FRS.

Risk models are valuable tools for risk classification in patients with long-term follow-up of stable CAD and for the evaluation of treatment alternatives. It is important to raise patient awareness of long-term healthy lifestyle by proposing that patients at intermediate risk exercise, eat healthy, and quit smoking, but it is also important to identify and closely follow patients at high risk in order to provide intensive pharmacological treatment and, if necessary, revascularization to reduce cardiovascular risk. Although high-risk patients in current guidelines appear to be the focus of treatment alternatives, undoubtedly early-stage measures to be applied to low- and moderate-risk patients will narrow the high-risk patient population in the future.[18] In practice, predicting the presence and severity of vascular disease is important to establish the treatment strategy. In this respect, the FRS and PCRAE risk models are one step ahead of the SCORE risk model and can be useful tools for guiding invasive and noninvasive diagnostic tests and for determining treatment options.

Limitations

Our study has important limitations. First, the sample size was calculated according to the primary hypothesis of the study. However, the number is underpowered for individual risk factors to predict the presence of severe CAD in subgroup analyses. Second, risk assessment models were not implemented in the population with known CAD, because these patients are already considered a high-risk group. However, since the aim of the study was to compare the differential strengths of the risk scoring systems in patients known to be at high risk, the population selection is considered appropriate. Finally, it is a single center study and the sample consisted only of patients admitted to our hospital, which prevents the generalization of the results.

Conclusion

The commonly used FRS and SCORE risk scoring systems and the new PCRAE risk scoring system have significant differences in terms of their ability to detect high-risk patients. Although the PCRAE system seems to be superior to the others, the high likelihood of having CAD in the present study population should be kept in mind. The PCRAE system has been criticized for its low positive predictive value in the general population, making more people to be on statin treatment. Another important result of this study is that renal insufficiency or reduced eGFR alone were identified as strong predictors of the presence of severe CAD. Therefore, eGFR, which can be easily calculated, is an effective variable to be incorporated into new risk assessment systems.

Author contributions

Conception and design of the research: Gormel S, Barcin C. Acquisition of data: Gormel S. Analysis and interpretation of the data: Gormel S, Barcin C. Statistical analysis: Gormel S, Barcin C. Writing of the manuscript: Gormel S, Barcin C. Critical revision of the manuscript for intellectual content: Barcin C.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Gata Komutan Bilimsel Yardimciligi under the protocol number 50687469-1491-254-14/1684.4-561. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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