JMB 2009; 28 (3) DOI: 10.2478/v10011-009-0008-9

UDK 577.1 : 61 **ISSN 1452-8258**

JMB 28: 145–151, 2009

Original paper
Originalni naučni rad

EVALUATION OF CORONARY RISK SCORE APPLICATIONS IN 10-YEAR CORONARY HEART RISK ESTIMATION

ISPITIVANJE ZNAČAJA PRIMENE BODOVNIH SISTEMA ZA PROCENU UKUPNOG 10-GODIŠNJEG RIZIKA ZA KORONARNU BOLEST SRCA

Nevena Eremić, Mirjana Đerić

Center for Laboratory Medicine, Clinical Center of Vojvodina, Novi Sad, Serbia

Summary: Atherosclerosis is a multifactorial disease with risk factors that have multiple effects. In the identification and treatment of asymptomatic individuals at high risk for developing coronary heart disease (CHD) different risk scoring schemes are used in everyday routine. The aim of this study was to compare SCORE recommended for our country with two other most frequently used risk schemes for 10-year CHD risk evaluation: Framingham and PROCAM as well as their modifications. From 220 examined subjects of both sexes, who were treated mainly for lipid metabolism disorder at the Dispensary for Atherosclerosis Prevention, Centre for Laboratory Medicine, Clinical Centre of Vojvodina, 110 subjects were included in our study and agreed to a one-year follow-up. At first check-up, 15% had low risk according to Framingham Weibull and 78% according to PROCAM, intermediate 12% according to PROCAM NS up to 45% according to Framingham Weibull, and high 8% according to PROCAM up to 40% according to Framingham Weibull. After a one-year treatment 30% were in the low risk category according to Framingham Weibull and 88% according to PROCAM. Intermediate from 10% according to PROCAM to 36% according to Framingham Weibull, and high from 2% according to PROCAM to 25% according to Framingham Weibull. There is a significantly lower percentage of high risk individuals and a higher percentage of low risk individuals after one year of lipid disorder treatment.

Keywords: coronary heart disease, risk factors, risk estimation, hyperlipidemia

Kratak sadržaj: S obzirom na to da je ateroskleroza multifaktorijalna bolest, u cilju identifikacije i lečenja asimptomatskih osoba s visokim rizikom za razvoj koronarne bolesti srca (KBS) u praksi se koriste različiti bodovni sistemi za procenu rizika. Cilj ovog istraživanja je da se izvrši upoređivanje SCORE bodovnog sistema preporučenog za našu sredinu sa ostala dva najčešće korišćena bodovna sistema za procenu 10-godišnjeg rizika za KBS: Framinghamskog i PROCAM sistema, kao i njihovih modifikacija. Od 220 pregledanih ispitanika oba pola, upućenih u Ambulantu za prevenciju ateroskleroze Kliničkog centra Vojvodine prvenstveno radi lečenja lipidskog poremećaja, 110 je uključeno u našu studiju i praćeno godinu dana. Prilikom prvog pregleda, osoba s niskim rizikom je bilo od 15% prema skoru Framingham Weibull do 78% prema skoru PROCAM, srednjim od 12% prema PROCAM NS do 45% prema Framingham Weibullu, a visokim od 8% prema PROCAM-u do 40% prema Framigham Weibullu. Posle godinu dana lečenja, u kategoriji niskog rizika bilo je od 30% prema Framingham Weibullu do 88% prema PROCAM-u, srednjeg od 10% prema PROCAM-u do 36% prema Framingham Weibullu, a visokog od 2% prema PROCAM-u do 25% prema Framingham Weibullu. Kako su lipidski parametri značajni kriterijumi svih bodovnih sistema za procenu rizika od KBS, ustanovljeno je očekivano signifikantno sniženje broja ispitanika u kategoriji visokog, a povećanje u kategoriji niskog rizika posle godinu dana lečenja lipidskog poremećaja, procenjivano prema svim ispitivanim bodovnim sistemima.

Ključne reči: koronarna bolest srca, faktori rizika, procena rizika, hiperlipidemija

Address for correspondence:

Dr Nevena Eremić
Clinical Center of Vojvodina
Center for Laboratory Medicine
Hajduk Veljkova 1
21000 Novi Sad, Serbia
Tel: 021 484 3992
e-mail: nevenaer@gmail.com

List of abbreviations:

CHD – coronary heart disease; CVD – cardiovascular disease; NCEP – National Cholesterol Education Program; ATP III – Adult Treatment Panel III; SCORE – Systemic Coronary Risk Evaluation Project; FRS – Framingham risk score; PROCAM – The Prospective Cardiovascular Munster Study.

Introduction

The principle of coronary heart disease, which is one of the major causes of morbidity and mortality, is premature atherosclerosis (1). The need of identifying risk factors for atherosclerosis in the process of early detection has gained much attention in recent years. Despite that, major independent risk factors, which have been identified in the last fifty years (smoking, hypertension, elevated level of total cholesterol or LDL fraction, low HDL cholesterol, diabetes, progressing age), are still mostly incorporated in the majority of coronary risk scores for 10-year coronary heart disease risk estimation that were recommended by American (National Cholesterol Education Program), European (Third and Fourth Joint Task of European Society of Cardiology and other societies) as well as independent (International Task Force for Prevention of Coronary Heart Disease) societies (1–4). Coronary risk scores were constructed as the end point result of processing data from numerous epidemiological studies with a view to estimate risk and identify asymptomatic persons at high risk for development of premature atherosclerosis (5).

The most commonly used risk scores are Framingham, PROCAM, SCORE and their modifications.

As a definitive result of the Framingam Heart Study, the first risk score for estimation of 10-year coronary heart disease risk was designed in 1991. Risk factors that were incorporated in estimation were: age, level of total serum cholesterol, HDL cholesterol, systolic and diastolic blood pressure, diabetes and smoking. A certain number of points is obtained while estimating every single risk factor and then calculated according to a particular table whereupon the 10-year CHD risk is estimated as percentage (6, 7).

National Cholesterol Education Program (NCEP) has accepted the Framingham risk score (FRS) and modified it for its guideline Adult Treatment Panel III (ATP III) 2001. Modified FRS is very similar to the original, based on the same principles however, there are differences in age intervals and diastolic blood pressure is not considered. In modified FRS diabetes is not included directly in point scoring, because it is considered that all diabetic patients have high risk (>20%) and diabetes is CHD risk equivalent. Besides the two classic FRS, there is a computer interactive Framingham Weibull model. The risk factor that distinguishes this coronary risk score from the former two is the estimation of the presence of left ventricular hypertrophy (2, 4).

PROCAM risk score is designed as the final result of the Prospective Cardiovascular Munster Study (PROCAM) and includes 8 independent risk factors: age, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, smoking, diabetes, positive family history of myocardial infarction in the first generation before the age of 60 years. Although PROCAM study included only the male population, there is a possibility of application of this risk score in females (4, 8, 9).

Using the data on morbidity and mortality of CHD from the MONICA study for the city of Novi Sad, the PROCAM NS coronary risk score is obtained (10).

Besides the classical schematic model, PROCAM risk score can also be designed for computer use when it is called PROCAM Cox proportional hazards model (10).

In the third and fourth European guidelines for CVD prevention, that were published in 2003 and 2007, Systemic Coronary Risk Evaluation Project (SCORE) is recommended for 10-year risk estimation for first fatal CVD event of atherosclerotic origin in contrast to other risk scores which are used for estimation of total CHD risk (fatal and non-fatal). Risk factors that were included in estimation are gender, age, smoking, systolic blood pressure and total cholesterol. There are separate schemes for high and low risk regions for CHD. Our country is in the high risk region.

Unlike other risk scores, where the risk for 10-year CHD risk estimation is high > 20%, intermediate 10–20% and low < 10% in SCORE that limit is >5%, 1–5% and <5% (3,11–13). According to Conlusions of our Consensus Conference for Alteration of Lipid Reference Values and Target Values for Lipid Disorder Treatment from 2005 the SCORE scheme with corrections from the MONICA study is suggested for 10-year CHD risk estimation (14).

Considering that up to this day, recalibration of SCORE schemes has not been finished, the aim of this study is to assess the comparison of most commonly used coronary risk scores for 10-year CHD risk estimation, FRS and PROCAM with suggested SCORE risk score, as well as to evaluate their practical application in everyday clinical routine.

Material and Methods

This study was performed as a retrospective-prospective study during one year. From 220 examined subjects of both sexes, who were treated mainly for lipid disorder at the Dispensary for Atherosclerosis Prevention of the Centre for Laboratory Medicine of the Clinical Centre of Vojvodina, 110 persons developed CHD or CHD equivalent (diabetes, peripheral arterial disease, abdominal aortic aneurism or carotid artery disease). All risk scores qualify these persons as being in the high risk category for CHD development.

From 110 other subjects there were 39 (34.45%) males and 71 (64.55%) females. Patient history and the weight (kg), height (cm), waist circumference (cm) as well as blood pressure (mmHg) were obtained for

every subject. The evaluation was also made in relation to actual lipid disorder (lipid parameters). Concentrations of total cholesterol and triglycerides were determined in serum taken after a fasting period of 12 hours by standard biochemical methods (Tecnicon RA-XT, BioMerieux), while HDL cholesterol was determined by the direct method using RANDOX reagents (15). The data were analysed at first examination and after one year of lipid disorder treatment. The 10-year CHD risk was evaluated in every single subject using seven different risk scoring schemes. Observed risk factors were gender, age, lipid parameters, bood pressure, positive family history and smoking.

Within FRS, point scoring was done using the original, modified according to ATP III, as well as the computer interactive model (Weibull model) which includes presence of left ventricular hypertrophy (10).

PROCAM risk score was used as a classical schematic model that was adapted for the computer called Cox proportional hazards model and PROCAM NS (10).

PROCAM risk score was designed for males but can be used for females in postmenopause. The evaluation is done by dividing the risk obtained for males by four. PROCAM risk score can be modifed according to the MONICA study. Total number of points is multiplied with conversion factor and then 10-year CHD risk estimation is determined according to the final sum of points. Conversion factor according to the MONICA study for Novi Sad for males is 1.37 and for females 1.24.

For 10-year CHD risk estimation according to the SCORE risk score sistem, risk schemes for high risk European regions were used. Schemes were separate for males and females. For every single subject a field that is close to its age, level of total cholesterol and systol blood pressure is used. In that field a number which indicates a percentage of 10-year CHD risk is already written.

Microsoft Excel 2003 was used to evaluate the statistical data. The statistical functions that were used are average, standard deviation, percentage difference and Student T-test (16).

Results

The basic characteristics of examined subjects obtained were shown in *Table I*. In the observed group, the percentage of females was higher ($p<0.001$) and they were significantly older in comparison with males ($p<0.02$). From all other obtained values, only significantly higher levels of HDL cholesterol were noticed in females (*Table I*).

Using seven different coronary risk scores for 10-year CHD risk evaluation in our patients at first examination it is observed that the percentage of subjects with low risk varies from 15% according to Framingham Weibull to 78% according to PROCAM, with intermediate risk from 12% according to PROCAM to 45% according to Framingham Weibull, and with high risk from 8% according to PROCAM to 40% according to Framingham Weibull (*Table II*).

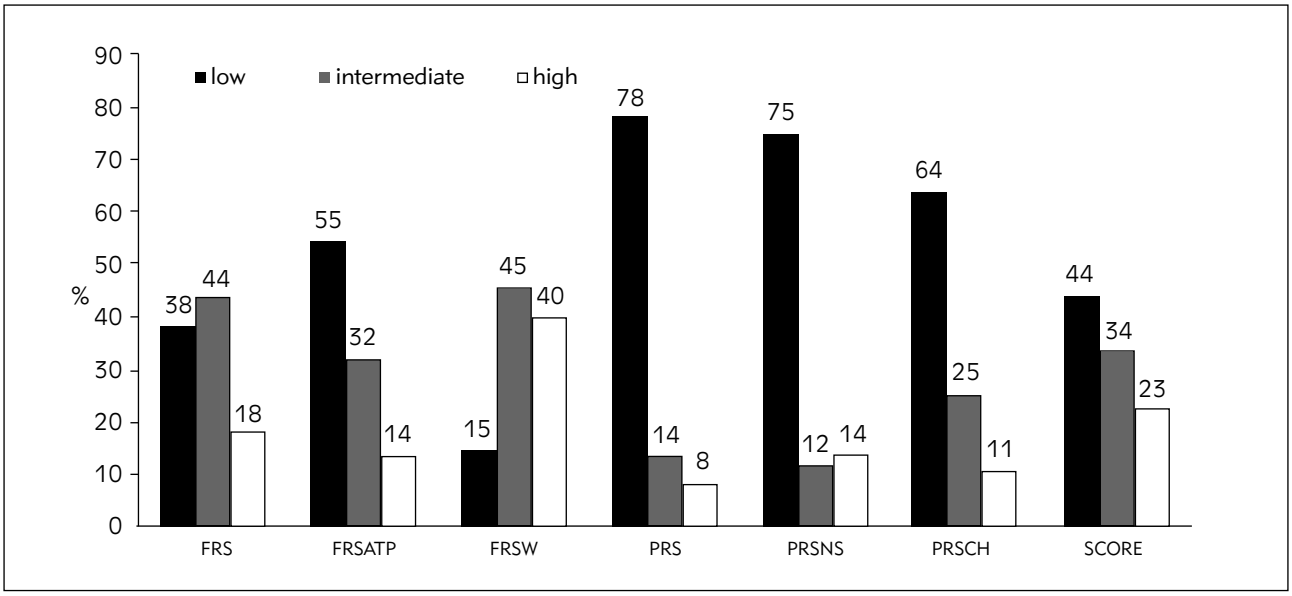

Figure 1 The percentage distribution of three 10-year coronary risk categories estimated according to different coronary risk scores at first examination.

Abbreviations: FRS – Framingham risk score; FRS ATP – ATP III modified Framingham risk score; FRS W – computer model of the Framingham risk score; PRS – PROCAM risk score; PRS NS – PROCAM risk score modified according to the MONICA study; PRS CH – computer model of the PROCAM risk score; SCORE – SCORE risk score.

Table I Basic characteristics of the studied subject group.

	Total	Male	Female
Number (%)	110	39 (34.45)	71 (64.55) ***
Age (year)	54.51 ± 10.13	51.41 ± 11.24	56.21 ± 9.11**
BMI (kg/m^2)	26.69 ± 3.34	27.04 ± 2.48	26.56 ± 3.74
Systolic BP (mmHg)	87.50 ± 11.83	128.33 ± 10.96	132.68 ± 17.31
Diastolic BP (mmHg)	131.1 ± 15.45	81.67 ± 7.81	82.61 ± 9.74
Fasting glucose (mmol/L)	5.33 ± 0.69	5.35 ± 0.71	5.31 ± 0.69
Total C (mmol/L)	7.29 ± 1.41	7.04 ± 1.41	7.43 ± 1.40
Triglycerides (mmol/L)	2.28 ± 1.05	2.30 ± 1.03	2.25 ± 1.07
HDL C (mmol/L)	1.23 ± 0.37	1.08 ± 0.24	1.31 ± 0.39***

BP – blood pressure; BMI - body mass index; C – cholesterol ; *** – p<0.001; ** – p<0.02.
Values are presented as mean values ± standard deviation.

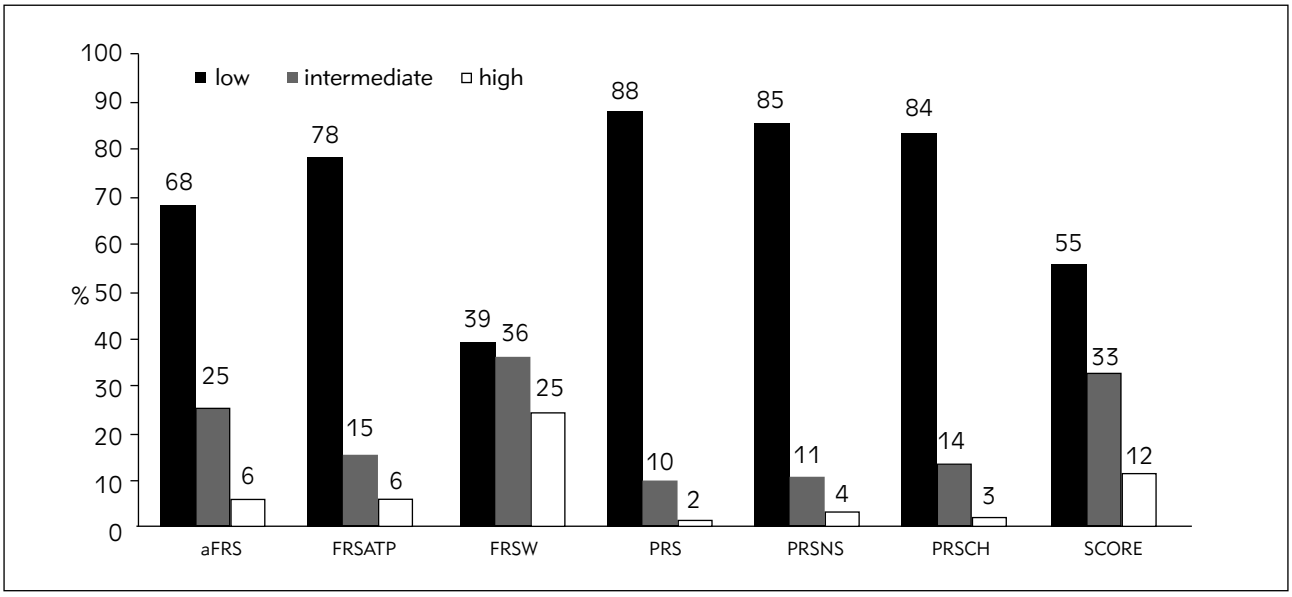

Figure 2 The percentage distribution of three 10-year coronary risk categories estimated according to different coronary risk scores after one-year lipid disorder treatment.

Abbreviations are the same as in *Figure 1*.

After a one-year lipid disorder treatment there were 39% of subjects with low risk (Framingham Weibull) or up to 88% (PROCAM); intermediate from 10% (PROCAM) to 36% (Framingham Weibull); and high risk from 2% (PROCAM) to 25% (Framingham Weibull) (*Figure 2*).

At the first examination, in the low risk category there were statistically significant differences in risk category distribution among our patients, using all obtained risk scores, except between Framingham ATP III and PROCAM Cox Hazards and SCORE as well as between PROCAM and PROCAM NS and PROCAM NS and PROCAM COX Hazards.

In the intermediate risk category there were statistically significant differences in risk category distribution among our patients, using all risk scores except among all enquired Framingham and PROCAM risk scores, as well as between SCORE and PROCAM and PROCAM Cox Hazards. Framingham Weibull was significantly different from all other obtained risk scores.

In the high risk category there were significant differences between Framingham Weibull in comparison with Framingham ATP III, PROCAM, PROCAM NS, PROCAM Cox Hazards and SCORE. There were significant differences between Framingham and PROCAM, PROCAM and SCORE and PROCAM Cox Hazards and SCORE (*Table II*).

Table II Statistical differences among estimated 10-year coronary risk score categories at first examination.

	FRS			FRS III			FRS W			PRS			PRS ns			PRS ch			SCORE		
	LR	IR	HR	LR	IR	HR	LR	IR	HR	LR	IR	HR	LR	IR	HR	LR	IR	HR	LR	IR	HR
FRS	-	-	-	d	n	n	a	n	a	a	a	e	a	a	n	a	b	n	a	b	n
FRS III	d	n	n	-	-	-	d	e	a	a	b	n	a	a	n	n	n	n	n	n	n
FRS W	a	n	a	a	e	a	-	-	-	a	a	a	a	a	a	d	e	a	a	e	d
PRS	a	a	e	a	b	a	a	a	a	-	-	-	n	n	n	d	e	n	a	e	b
PRS ns	a	a	n	b	a	a	a	a	a	n	n	n	-	-	-	n	d	n	a	d	n
PRS ch	a	b	n	n	n	a	c	e	a	d	e	n	n	d	n	-	-	-	b	n	c
SCORE	a	n	n	n	n	d	a	a	d	a	a	b	a	a	n	b	n	c	-	-	-

Abbreviations: a – p< 0.001; b – p< 0.005; c – p< 0.02; d – p <0.01; e – p< 0.05; n – p>0.05; FRS – Framingham risk score; FRS III – ATP III modified Framingham risk score; FRS W – computer model of Framingham risk score; PRS – PROCAM risk score; PRS ns – PROCAM risk score modified according to the MONICA study; PRS ch – computer model of PROCAM risk score; SCORE – SCORE risk score.

Table III Statistical differences among estimated 10-year coronary risk score categories after a one-year lipid disorder treatment.

	FRS			FRS ATP			FRS W			PRS			PRS ns			PRS ch			SCORE		
	LR	IR	HR	LR	IR	HR	LR	IR	HR	LR	IR	HR	LR	IR	HR	LR	IR	HR	LR	IR	HR
FRS	-	-	-	n	n	n	a	n	a	a	a	n	b	a	n	d	b	n	n	n	n
FRS III	n	n	n	-	-	-	a	e	a	e	b	n	n	a	n	n	n	n	a	n	n
FRS W	a	n	a	a	e	a	-	-	-	a	a	a	a	a	a	a	e	a	a	a	c
PRS	a	a	n	e	b	n	a	a	a	-	-	-	n	n	n	n	e	n	a	a	b
PRS ns	b	a	n	n	a	n	a	a	a	n	n	n	-	-	-	n	d	n	a	a	b
PRS ch	d	b	n	n	n	n	a	e	a	n	e	n	n	d	n	-	-	-	a	n	d
SCORE	n	n	n	a	n	n	a	a	c	a	a	b	a	a	b	a	n	d	-	-	-

Abbreviations are the same as in *Table II*.

After a one-year lipid disorder treatment, there were significant differences in the low risk categories between Framingham and all PROCAM risk scores as well as between Framigham Weibull and all other enqired risk scores.

After one-year treatment testing, there were no significant differences in the distribution frequency in the intermediate risk category between Framingham risk score and Framingham ATP III and Framingham Weibull, as well as between Framingham ATP III and PROCAM, PROCAM NS and PROCAM Cox Hazards. There were also no significant differences among all three PROCAM risk scores (*Table III*).

In the high risk category, after a one-year lipid disorder treatment, Framingham Weibull significantly differs from all other enquired risk scores as well as SCORE in comparison with the other three PROCAM risk scores.

Discussion

The principle of coronary heat disease is atherosclerosis. Concerning no unique etiological factor, the management against atherosclerosis development is targeted on factors which contribute to the development of this disease. Many individual characteristics contribute to the risk of development of CHD including gender, age, blood pressure, glucose tolerance, smoking and concentrations of lipids. The complex relationship between these factors makes individual assessment in everyday clinical routine very difficult, which is why coronary risk scores were made (1). According to our Consensus Conference in 2005 (14) the SCORE risk scheme modified according to the results from MONICA study (10), which has not been done up to now, has been recommended for use, so we decided to make a comparison with the other two most frequently used risk scores, Framingham (original, modified according to ATP III and the computer Weibull model) and PROCAM (original, modified according to the MONICA study and the computer Cox Hazards model).

In our group there was a higher percentage of older females than males. No similar studies were performed in our country on dislipidemic population patients, while in Spain there was a similar study for age and gender structure correspondents (17).

In three studies, Vekić et al. (18), Jovičić et al. (19) and Cristobala et al. (17) the mean values of systolic and diastolic blood pressure were similar to values in our subjects. There were no significant differences between gender in our study and the three other compared studies.

Our study was performed on patients who were sent to the Dispensary for Atherosclerosis Prevention, Centre for Laboratory Medicine, Clinical Centre of Vojvodina, mainly for the lipid metabolism disorder treatment, therefore the mean values of lipid parameters except HDL cholesterol are higher in our subjects in comparison to other similar studies (17–19).

It can be noticed that there are significant differences present in CHD risk category distribution when using different risk scores. According to our results, it can be concluded that the Framingham Weibull model has the most severe classification criteria (*Figure 1* and *Figure 2*). Framingham Weibull is an interactive model designed for the computer. It differs from the other classical Framingham risk scores because it is constructed using a continual variable opposite to discontinual. Besides the classical risk factors that are included in other risk scores such as age, gender, systolic blood pressure, ratio between total and HDL cholesterol, smoking and presence of diabetes, the presence of left ventricular hypertrophy is considered. This could explain more severe classification criteria in relation to other risk scores (20).

According to our results, it can be concluded that PROCAM risk score is the weakest, with the highest frequency of low CHD risk individuals. Unlike Framingham risk score which is used for the probability estimation of coronary death development, myocardial infarction, stable and non-stable angina pectoris, PROCAM is designed for the risk estimation of coronary death or first myocardial infarction within 10 years (21). It is designed for the male population, therefore not critical enough for the female population because it underestimates the risk for CHD. Because of the high percentage of female population (64.55%) in our subject group, the percentage distribution of different risk categories using this coronary risk score cannot be valid.

After the one-year lipid disorder treatment there is a significant reduction in proatherogenic lipid parameters. Concerning that they are important constituents of every risk score, we also noticed a significantly lower percentage of high risk individuals and a higher percentage of low risk individuals, which might be very important for the motivation of our patients.

All risk scores have their advantages and disadvantages. Interactive computer models are more precise because continual variables are included as opposite to other schemes. It is also more convenient than using schemes and calculating the risk for every patient.

References

1. Ostojić M. Preporuke za prevenciju ishemijske bolesti srca. Prvo izdanje, Beograd: Ministarstvo zdravlja republike Srbije; 2002.
2. The Expert Panel. The Third Report of the National Cholesterol Education Program (NCEP), Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Tratment Panel III). Final report. Circulation 2002; 106: 3143–421.
3. Backer G, Ambrosioni E, Borch-Johansen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third joint task force of European and other societies on cardiovascular prevention in clinical practice. Eur J Cardiovas Prev Rehabil 2003; 10 (Suppl 1) S1–78.
4. International Task Force for Prevention of Coronary Heart Disease. Pocket Guide to Prevention of Coronary Heart Disease, 1st ed. Grunnnald: 2003.
5. Grundy SM, Cleeman JI, Mertz NB, Brewer B, Clark L, Hunninghake D, et al. Implications of recent clinical trials for National Cholesterol Education Program Adult Treatment Panel III Guidelines. JACC 2004; 44 (3): 720–32.
6. National Heart Lung and Blood Institute. Framingham Heart Study. http://www.nhlbi.nih.gov/about/framingham/index.html (05/10/2008).
7. Sarti C, Gallagher J. The metabolic syndrome. J Diabetes Complicat 2006; 20 (2): 121–32.
8. Assman G, Cullen P, Shulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the Prospective Cardiovascular Munster (PROCAM) study. Circulation 2002; 105: 310–15.
9. Assman G, Cullen P, Shulte H. The Munster Heart Study (PROCAM): Results of follow-up at 8 years. Eur Heart J 1998; 19 (Suppl A): A2–A11.
10. International Task Force for Prevention of Coronary Heart Disease. http:// www.chd-taskforce.com (05/10/ 2008).
11. Conroy RM, Pyörälä K, Fitzgerald AP, Sams S, Meniotti A, Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE Project. Eur Heart J 2003; 24: 987–1003.
12. Erhardt LR, Gotto A. The Evolution of European Guidelines: changing the management of cholesterol levels. Atherosclerosis 2006; 185 (1): 12–20.
13. Graham I, Atar D, Borch-Johansen K, Boysen G, Burrel G, Cifkova R, et al. European guidelines on cardiovascular disease prevention in clinical practice. Eur J Cardiovas Prev Rehabil 2007; 14 (Suppl 2) S1-113.

14. Zamaklar M. Konsenzus konferencija o promeni referentnih vrednosti lipida i ciljnim vrednostima lipidskih poremećaja. Jugoslov Med Biohem 2005; 24: 299–300.

15. Third Report of the National Cholesterol Education Programme (NCEP). Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA Publications 2001; 285 (19): 2486–97.

16. Grujić V, Jakovljević Đ, eds. Primena statistike u medicinskim istraživanjima. Prvo izdanje. Novi Sad: Medicinski fakultet; 1998.

17. Cristobal J, Lago F, De la Fuente J, Gonzalez-Juanatey J, Vazquez-Belles P, Vila M. Comparison of Coronary Risk Estimation Derived Using the Framingham and REGICOR Equations. Rev Esp Cardiol 2005; 58 (8): 910–5.

18. Vekić J, Topić A, Zeljković A, Jelić-Ivanović Z, Spasojević-Kalimanovska V. LDL and HDL subclasses and their relationship with Framingham risk score in middle-aged Serbian population. Clin Biochem 2007; (40): 310–6.

19. Jovičić S, Ignjatović S, Majkić-Singh N. Comparison of two different methods for cardiovascular risk assessment: Framingham Risk Score and SCORE System. Journal of Med Bioh 2007; 26 (2): 94–7.

20. Topol EJ, Lauer M. The rudimentary phase of personalised medicine: coronary risk scores. Lancet 2003; 362: 1776–7.

21. Empana JP, Ducimetriere P, Arveiler D, Ferrieres J, Evans A, Ruidavets JB, et al. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? Eur Heart J 2003; 24: 1903–11.

Received: January 10, 2009

Accepted: April 3, 2009