

THE “FIVE RISKS ALGORITHM”: AN EASY TOOL FOR CARDIOVASCULAR RISK ESTIMATION

Dirk Devroey, Jan Vandevoorde

Department of General Practice, Vrije Universiteit Brussel, Brussels, Belgium

SUMMARY

The aim of this study is to provide an easy tool to identify patients with a high cardiovascular risk, especially those qualifying for lipid-lowering treatment. The decision to treat with lipid-lowering drugs was assessed with five new risk algorithms. The Five Risk algorithm (5R) takes into account male gender, high systolic blood pressure, high total cholesterol, smoking and high blood sugar as independent risk factors. Patients with three independent risk factors qualify for lipid-lowering treatment. Compared to the Framingham Risk Score, the 5R has a Kappa coefficient of 0.62. Compared to the SCORE, the Six Risk algorithm (6RDF) has a Kappa coefficient of 0.70. The 6RDF uses only four independent risk factors (male gender, high systolic blood pressure, high total cholesterol and smoking) but having diabetes or a family history of premature coronary heart disease are exclusion criteria for which treatment with lipid-lowering drugs is always indicated.

Key words: cardiovascular risk, cardiovascular diseases, primary prevention, cholesterol, blood pressure, diabetes

Address for correspondence: D. Devroey, Department of General Practice, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium.
E-mail: dirk.devroey@vub.ac.be

INTRODUCTION

The identification of patients with a high cardiovascular risk is an essential step in the prevention of cardiovascular diseases. Several algorithms are used. All these algorithms use different risk factors, different cut-off points and different exclusion factors. Furthermore, most of the algorithms are based on local populations making, extrapolations to other populations little reliable (1–3).

The two most commonly used risk algorithms are the Framingham Risk Score (FRS) and the European Systemic COronary Risk Evaluation (SCORE) system.

The FRS is based on a small population in the north-east of the United States and estimates the risk of developing a coronary heart disease over the course of ten years (4). Tables for patients with and without diabetes are provided and the risk of developing a coronary heart disease (CHD) is estimated. Correction factors for patients with a family history of premature CHD, high triglycerides or low HDL-cholesterol are used. The Framingham algorithm estimates the risk for coronary events only and suggests lipid-lowering treatment for an estimated risk of 20% or more.

The SCORE system is based on different populations all over Europe and estimates the risk of dying from cardiovascular disease in the next ten years (5). Tables with total cholesterol and with the ratio of total cholesterol over HDL-cholesterol exist. No correction factors are used but existing cardiovascular disease, diabetes, family history, and very high levels of total cholesterol, LDL-cholesterol and blood-pressure are used as exclusion criteria. The SCORE system estimates the risk for total cardiovascular mortality and suggests lipid-lowering treatment for an estimated risk of 5% or more.

To facilitate the assessment of these risk factors, algorithms

have been incorporated into the guidelines. The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (NCEP ATP III) guidelines use the FRS (4), while the Third Joint European guidelines use the more recently developed SCORE (5). Important differences exist not only between the risk algorithms but also between the regional guidelines for lipid-lowering treatment. The NCEP ATP III guidelines recommend screening all adults without CHD every 5 years. The European guidelines recommend screening all men aged 55 years or older and all women aged 65 years or older with any individual risk factor or with close relatives with premature CHD. Many other algorithms such as the New-Zealand algorithm (6) and the Sheffield tables exist (7). Although all these algorithms try to estimate risks as accurately as possible, subjects qualifying for lipid-lowering treatment differ substantially between algorithms (1–3, 8–10).

Gender, blood pressure, total cholesterol, smoking and diabetes are included in most of the algorithms. However, patient history, family history of premature CHD, physical inactivity, high calorie diet, obesity, triglycerides and HDL-cholesterol are often omitted from the risk estimation. Therefore, we can question their precise estimation of cardiovascular risk. Although it might help to stimulate patients, the reliability of the risk estimations is very low. Thereupon, the precise estimation of cardiovascular risk is very time-consuming and often needs the use of computers or electronic devices.

The aim of this study is to provide an easy tool to identify patients needing lipid-lowering treatment but without a precise estimation of cardiovascular risk in figures.

Table 1. The tested risk algorithms

	Male gender	Blood pressure	Cholesterol	Smoker	Diabetes	Family history
5R	+	+	+	+	+	-
5RD	+	+	+	+	EC*	-
6R	+	+	+	+	+	+
6RD	+	+	+	+	EC*	+
6RDF	+	+	+	+	EC*	EC*

*EC = exclusion criterion for which lipid-lowering treatment is always indicated.

MATERIAL AND METHODS

Study Population and Design

Data were collected in three small Belgian towns (Hoeilaart, Merchtem and Overijse). In total 12,756 inhabitants aged between 45 and 64 years were invited by the local authorities to visit their general practitioner for a cardiovascular check-up and blood test. An information campaign in the local press had been set up in order to augment the recruitment. All local family physicians (n=50) agreed to participate in the screening and received the study protocol.

A previous study using this entire study population focussed on the preventive interventions by family physicians (11). The present study was limited to participants without a cardiovascular history.

Two questionnaires had to be completed. The first was completed by the participant and concerned smoking behaviour, medical history and pharmaceutical treatment. The questionnaire was checked by the family physician and the missing answers were completed together with the participant during the health check-up.

During the first visit the second questionnaire was completed by the family physician and included blood pressure, weight, length and waist circumference, cardiovascular history and risk factors, and current treatment. A venous blood sample was collected after the participant had fasted for 12 hours. Blood sugar, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were determined.

The second visit was planned after an interval of two weeks. During that visit, the blood pressure was measured again and the results of the blood analysis were discussed. For blood pressure analysis we used the mean values from the first and the second visit. Blood pressure measurements were performed with a sphygmomanometer on the left upper arm of sitting patients after they had rested for at least five minutes.

Laboratory Testing

Serum TC, TG and HDL-C were measured enzymatically. Low-density lipoprotein cholesterol (LDL-C) levels were calculated with the Friedewald formula, unless TG levels were above 400 mg/dl (12). In that case LDL-C levels were measured enzymatically. All measurements were done by local laboratories. The quality of their measurements is guaranteed by the fact that they are, according to the Belgian rules for clinical biology, regularly

subjected to internal as well as external quality control. No central lab was used because the absolute value of the lipids and the other tests was of minor importance.

Tested Risk Algorithms

Firstly, patients needing cholesterol-lowering treatment were identified with the FRS and the SCORE. Two versions of SCORE exist: one for the high-risk regions and one for the low risk regions. The SCORE algorithm for the low-risks regions is recommended for Belgium and was used in our study.

Secondly, the decision to treat with lipid-lowering drugs was assessed with five new risk algorithms (5R, 5RD, 6R, 6RD, 6RDF) based on the occurrence of at least three out of six dichotomized risk factors (male gender, high systolic blood pressure (≥ 140 mmHg), high total cholesterol (≥ 190 mg/dl), smoking, diabetes and family history of premature CHD). Male gender, blood pressure, total cholesterol and smoking were always taken into account as independent risk factors. Diabetes and family history of premature CHD were also taken into account as independent risk factors or as exclusion criteria for which lipid-lowering treatment is always indicated (Table 1).

Finally, the decision to treat with lipid-lowering drugs based on the FRS and the SCORE was compared with the new risk algorithms.

Ethical Approval

The ethical review board of the Flemish Institute for General Practice (Vlaams Huisartsen Instituut; VHI) approved the study protocol.

Statistical Analysis

SPSS-PC 15® (SPSS Inc., Chicago, IL, USA) was used for analysis and statistical processing. The sensitivity and specificity of different combinations of risks factors were calculated. The overall agreement between FRS and SCORE was assessed using kappa statistics. Kappa represents the agreement between the two categorization schemes in excess of the amount of agreement that we would expect by chance. A kappa value of 1 indicates perfect agreement, while a kappa value of 0 indicates that agreement is no better than chance. Landis and Koch have proposed the following as standards for strength of agreement for the kappa coefficient: 0.01–0.20=slight, 0.21–0.40=fair, 0.41–0.60=moderate, 0.61–0.80=substantial and 0.81–1=almost perfect agreement (13).

Table 3. Sensitivity and specificity of risk algorithms compared to the Framingham score

	A	B	C	D	Sens	Spec	PPV	NPV	Kappa
SCORE	120	133	60	595	0.667	0.817	0.474	0.908	0.42
5R	129	62	51	666	0.717	0.915	0.675	0.929	0.62
6R	141	100	39	628	0.783	0.863	0.585	0.942	0.57
5RD	130	72	50	656	0.722	0.901	0.644	0.929	0.60
6RD	142	108	38	620	0.789	0.852	0.568	0.942	0.56
6RDF	143	160	37	568	0.794	0.780	0.472	0.939	0.46

RESULTS

Study Population

Of a total of 12,756 invited persons only 935 persons (7%) showed up. Twenty-seven persons with a history of a cardiovascular disease are excluded. In total 908 patients aged between 45 and 64 yr and without cardiovascular disease are included (550 women and 358 men). The mean age for men as well as for women is 56 years (SD=6). In total 14% of the participants are smokers, 36% have systolic hypertension (systolic blood pressure ≥ 140 mmHg) or are treated for it, 81% have hypercholesterolemia (TC ≥ 190 mg/dl) or are treated for it and 5.5% have diabetes (fasting glucose ≥ 126 mg/dl) or are treated for it. Sixteen percent of the participants have a family history of premature CHD.

Conventional Risk Estimations

In total, 20% of the patients (N=180) fulfil the criteria for lipid-lowering treatment according to the FRS and 28% (N=253) according the SCORE. Only 13% (N=120) fulfil the criteria for both algorithms (Table 2).

Compared to the FRS, the SCORE has a sensibility of 67% and a specificity of 82% corresponding with a positive predictive value (PPV) of 47% and a negative predictive value (NPV) of 91%. This means that the SCORE detects 120 subjects out of the 180 detected with the FRS. The SCORE detects 133 subjects not qualifying for treatment according to the FRS and 60 qualify with the FRS but not with the SCORE.

Compared to the SCORE, the FRS has, a specificity of 47% and a specificity of 91% corresponding with a PPV of 67% and a NPV of 82%. This means that the FRS detects 120 subjects out of the 253 detected with the SCORE. The FRS detects 60 subjects not qualifying for treatment with the SCORE and 133 qualify with the SCORE but not with the FRS. In the present study, a kappa value of 0.42 was obtained, indicating only a fair to moderate agreement between the FRS and SCORE algorithms.

Table 2. 2x2 table indicating the number of patients for which lipid-lowering treatment is indicated according to the Framingham and SCORE risk tables

	SCORE +	SCORE -	
FRS +	A=120	B=60	A+B=180
FRS -	C=133	D=595	A+D=728
	A+C=253	B+D=655	Total=908

Alternatives for the Framingham Score

Compared to the FRS, the 5R has a sensitivity of 72% and a specificity of 92% corresponding with a PPV of 68% and a NPV of 93%. The Kappa coefficient was 0.62 indicating a substantial agreement. The 5R takes into account male gender, high systolic blood pressure, high TC, smoking and high blood sugar as independent risk factors. Patients with three independent risk factors qualify for lipid-lowering treatment.

The 5R detects 129 subjects out of the 180 detected with the FRS. The 5R detects 51 subjects not qualifying for treatment according to the FRS and 51 qualify with the FRS but not with the 5R.

The sensitivity and specificity of the other tested risk algorithms are compared to the FRS in Table 3.

It is remarkable that, compared to the 5R and the FRS, the four other risk scores also have a relatively high sensitivity and specificity, especially the 5RD. The Kappa coefficient was 0.60 indicating a moderate agreement. The 5RD takes into account diabetes as an exclusion criterion for which treatment with lipid-lowering drugs is always indicated.

Alternatives for the SCORE

Compared to the SCORE, the 6RDF has a sensitivity of 87% and a specificity of 87% corresponding with a PPV of 72% and a NPV of 94%. The Kappa coefficient was 0.70 indicating a substantial agreement. The 6RDF uses only four independent risk factors (male gender, high systolic blood pressure, high TC and smoking) but diabetes as well as a family history of premature CHD are exclusion criteria for which treatment with lipid-lowering drugs is always indicated.

The 6RDF detects 219 subjects out of the 253 detected with the SCORE. The 6RDF detects 84 subjects not qualifying for treatment with the SCORE and 34 qualify with the SCORE but not with the 6RDF.

The sensitivity and specificity of the other tested risk algorithms are compared to the SCORE algorithm in Table 4.

It is remarkable that, compared to 6RDF and SCORE, the two other risk scores (6R and 6RD) also have a relatively good sensitivity and specificity. The 6R takes into account all risk factors as independent risk factors. The 6RD takes into account diabetes as an exclusion criterion for which treatment with lipid-lowering drugs is always indicated.

Table 4. Sensitivity and specificity of risk algorithms compared to the SCORE algorithm.

	A	B	C	D	Sens	Spec	PPV	NPV	Kappa
Framingham	120	60	133	595	0.474	0.908	0.667	0.817	0.42
5R	115	76	138	579	0.455	0.884	0.602	0.808	0.37
6R	162	79	91	576	0.640	0.879	0.672	0.864	0.53
5RD	123	79	130	576	0.486	0.879	0.609	0.816	0.39
6RD	168	82	85	573	0.664	0.875	0.672	0.871	0.54
6RDF	219	84	34	571	0.866	0.872	0.723	0.944	0.70

DISCUSSION

The Use of Risk Algorithms in Family Medicine

Family practices are the ideal environment for a board screening for patients with a high cardiovascular risk. Although the screening algorithms are developed for use in family practice, only few physicians use the risk charts. A Belgian study concluded that 41% of family physicians underestimated the prevalence of high risk patients and that 80% considered TC as a good parameter to estimate the patients’ individual cardiovascular risk. In total 53% of the family physicians never used risk charts to estimate cardiovascular risk (14).

A Dutch study among family physicians confirmed that many barriers hamper the implementations of risk charts and that there is a need for a more time-efficient strategy to estimate cardiovascular risk (15).

Are Exact Values Necessary for Risk Estimation?

The main difference between the 5R and the 6RDF tested in this study on the one hand and the common risk estimations FRS and SCORE on the other hand is that the 5R and the 6RDF do not need exact values for blood pressure and TC. In the 5R and the 6RDF all risk factors are dichotomized, making the estimation of cardiovascular risk and the decision whether or not to treat much easier. The inconvenience is that the cardiovascular risk is not exactly determined. However, taking into account the huge differences in sensitivity and specificity between the different risk algorithms, the need for a precise risk estimation is questionable.

Thereupon, there is a high variability of the measurements of TC and blood pressure over time (16, 17). Measurements of blood pressure depend highly on the moment of the measurement, the previous physical activity and the emotional circumstances. For cholesterol measurements an important intra- and inter-individual variability also exists. Studies with triplicate measurements of risk factors have shown that 30% of patients who should receive treatment with one measurement would be denied and 20% would receive unnecessary treatment (18). This is a new argument to question the very detailed risk estimations of the FRS and the SCORE.

Finally, the Third and Fourth Joint European Guidelines on cardiovascular disease prevention in clinical practice reject the concept of simply counting up cardiovascular risk factors (19, 20). They advice to quantify individual risk factors, as is known

in the FRS and the SCORE. However, the results of the present study suggest that in a low risk population, which is often found in primary health care, adding up individual cardiovascular risk factors has a good sensitivity and specificity to predict the need for lipid-lowering treatment.

Sensitivity of Framingham and SCORE

The FRS is accurate in estimating risk in populations where the average CHD risk is similar to the Framingham cohort (21). But under- and overestimates are seen in some European populations such as Germany, Italy, Austria, the United Kingdom and France (8, 9, 22–24).

Important differences in sensitivity and specificity between the FRS and the SCORE are not surprising. In our study, much more subjects were selected for treatment with the SCORE than with the FRS because the SCORE advises treatment for all subjects with a family history of premature CHD. Most of the patients selected for treatment with the FRS and not with the SCORE were non-smoking men with low blood pressure and TC superior to 220 mg/dl. These patients should receive lipid-lowering treatment according to the FRS but only from age 63 according to the SCORE.

In Germany, the FRS and the SCORE were also compared. The authors suggest that compared to the FRS, the SCORE-HIGH, which is indicated for risk estimation in Germany, may overestimate risk of fatal CVD in Germany (8). Similar conclusions can be drawn from our study were we found compared to the FRS, a higher number of patients needing treatment with the SCORE-LOW, which is indicated in Belgium.

The sensitivity of algorithms to detect patients at risk, such as the Prospective Cardiovascular Munster (PROCAM) Study, the SCORE or the FRS is rather low. The majority of myocardial infarctions occur in the average risk population. Independent indicators of cardiovascular risk, such as the C-Reactive Protein and the intima-media thickness can lead to more clarity. Some authors suggest that a combination of risk factors and risk indicators is needed to improve the estimation of the individual risk (25, 26).

Many efforts have been made to identify high risk people and to reduce treatment of low risk people. The accuracy of several risk assessment methods in identifying patients at high CVD risk have been compared in the British population (27). Compared with a CVD risk of 20% over 10 years, the Sheffield table, the Joint British Societies Chart, and the New Zealand Chart had a sensitivity of 81%, 63% and 75%, respectively. All had a good specificity of 90%. The World Health Organization-International

Society of Hypertension (WHO-ISH) and the United States Joint National Committee VI (JNC-VI) methods had unacceptably low specificities and failed to differentiate between those at high and low risk (27).

In Italy, two different national risk functions, the CUORE Project algorithm and the risk function incorporated in the software Riscard 2002, have been compared to the FRS and the reimbursement criteria for statins set by the Italian National Health System. Both national algorithms gave lower risk estimations, in comparison with the FRS. A low concordance was found even between the two national algorithms. The study confirmed that using different risk functions can substantially change statin prescription rate and the identification of patients for lipid-lowering treatment (9).

Another study compared the estimation of CHD risk by the FRS and the Copenhagen risk score (CRS) using Dutch population data. The average 10-year risk for CHD was significantly different between the FRS (4.6%, SD 5.0) and the CRS (3.2%, SD 4.1) (10).

Which Alternative Risk Score to Chose?

The 5R has, compared to the FRS, the highest overall agreement. However the, four other risk scores also have a relatively high overall agreement, especially the 5RD.

Compared to the SCORE, the 6RDF has, the highest overall agreement. However, 6R and 6RD have also a relatively high overall agreement.

The choice for the 5R as an alternative for the FRS and the 6RDF as an alternative for the SCORE is not surprising. The 5R as well as the FRS use male gender, high systolic blood pressure, high TC, smoking and diabetes as independent risk factors. The 6RDF as well as the SCORE use male, gender, high systolic blood pressure, high TC and smoking as independent risk factors but diabetes as well as a family history of premature CHD are considered as exclusion criteria for which treatment with lipid-lowering drugs is always indicated.

Limitations of the Study

We are aware of the fact that we did not perform the study in a representative sample of the population. Of a total of 12,756 persons in the three towns, aged between 45 and 64 years, only 935 persons (7%) showed up. Because the invitations and questionnaires were made in Dutch only, the low participation rate may be related to the high proportion of non-Dutch speaking inhabitants, especially in Overijse and Hoeilaart. The low participation rate could also be a selection bias for those who already had reasons to worry about their health or perhaps for those who already were health-conscious. For that reason the figures concerning mean blood pressure, mean lipoproteins and mean fasting blood sugar are probably not representative of the total population. However, this was not the aim of this study.

The over-representation of women (60%) and the low proportion of smokers (14%) indicate that a health-conscious population with a low cardiovascular risk has been examined. However, this low-risk population is representative for the population screened in general practice. On the other hand, several other studies using community-based samples found high proportions of women (28, 29).

CONCLUSIONS

The huge difference in overall agreement between the FRS and the SCORE system makes the decision whether or not to treat with lipid-lowering drugs highly dependent on the used algorithm.

The 5R and the 6RDF are useful alternatives for the FRS and the SCORE algorithms respectively. Compared to the FRS, the 5R has a substantial overall agreement ($\text{Kappa}=0.62$). The 5R takes into account male gender, high systolic blood pressure, high TC, smoking and diabetes as independent risk factors. Patients with three independent risk factors qualify for lipid-lowering treatment.

Compared to the SCORE system, the 6RDF has a substantial overall agreement ($\text{Kappa}=0.70$). The 6RDF uses only four independent risk factors (male gender, high systolic blood pressure, high TC and smoking) but diabetes as well as a family history of premature CHD are considered as exclusion criteria for which treatment with lipid-lowering drugs is always indicated.

Both algorithms easily identify persons for which lipid-lowering treatment is necessary. Exact figures for blood pressure and cholesterol are not necessary.

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Conflicts of interest

D. Devroey has served as consultant and received travel expenses or funding for research from **the following** pharmaceutical companies (Merck Sharp & Dohme, Novartis and Bristol-Myers Squibb) that market cardiovascular drugs.

J. Vandevoorde has served as consultant and received travel expenses or funding for research from **the following** pharmaceutical companies (Novartis and GSK) that market cardiovascular drugs.

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