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The relationship between cardiovascular risk estimated by use of SCORE system and intima media thickness and flow mediated dilatation in a low risk population

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Abstract

Background: *The SCORE system is a simple, currently recommended method of cardiovascular risk assessment. The aim of this study is to determine the relationship between SCORE risk and intima media thickness (IMT) and flow mediated dilatation (FMD) in a low risk population.*

Methods: *119 people (59 men) without known cardiovascular disease and estimated by means of SCORE system risk < 5%, were included in the study. The ultrasound method was used to assess brachial artery diameter (BAd), FMD, nitroglycerin mediated dilatation (NMD) of brachial artery and IMT of common carotid. FMD × BAd and FMD/NMD indexes representing hyperemia-induced vasodilatation independent of brachial artery properties were analyzed.*

Results: *IMT measured was 0.52 ± 0.08 mm; FMD: 17.5 ± 7.8%; NMD: 27.0 ± 9.0%; FMD × BAd: 58.2 ± 22.4, FMD/NMD: 0.64 ± 0.19. Independent predictor for both FMD and NMD was BAd (R^2 –0.31; $p < 0.001$; R^2 –0.44; $p < 0.001$; respectively), for FMD × BAd index and FMD/NMD index was IMT (R^2 –0.04; $p = 0.02$; R^2 –0.04; $p = 0.015$) in a multivariate analysis. Risk estimated by use of the SCORE system was between 0 and 4% (median-1, 25––75 Q: 0–2). A relationship between SCORE risk and IMT (ANOVA $p < 0.001$), FMD (ANOVA $p < 0.001$), NMD (ANOVA $p < 0.001$), FMD × BAd index (ANOVA $p = 0.017$), but not FMD/NMD index (ANOVA $p = 0.27$), was found.*

Conclusions: *The association of a simple stratifying scale (SCORE system) with indices of early vascular remodeling in a low risk population supports its clinical significance.* (Cardiol J 2009; 16, 5: 407–412)

Key words: flow mediated dilatation, nitroglycerin mediated dilatation, intima media thickness, SCORE

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Introduction

Cardiovascular diseases are the leading cause of death in civilised countries, including Poland [1]. The SCORE system is a simple, currently recommended method of cardiovascular risk assessment [2, 3]. SCORE is the result of several European long-term prospective cohort studies recruiting altogether more than 200,000 individuals [2].

SCORE allows the evaluation of a ten-year risk of cardiovascular diseases death based on modifiable and unmodifiable risk factors, including: age, sex, systolic blood pressure (SBP) and serum concentrations of total cholesterol (TCh). While the limited number of estimated risk factors is its major advantage, on the other hand opponents point to the lack of several important risk factors, such as family history, low density lipoprotein cholesterol (LDL-Ch) level or obesity [4].

The SCORE-based estimated ten-year risk ≥ 5% indicate a high risk population. However, the most difficult challenge is to identify the patients at risk for cardiovascular events in a young low-risk population. The evaluation might be based either on the SCORE risk extrapolation for the age of 60 and relative risk or noninvasive methods assessing early structural and functional changes within arterial vessels. A large body of evidence supports the role of brachial artery flow mediated dilatation (FMD) and carotid artery intima-media thickness (IMT) in this setting. Unfortunately, previous studies have not provided sufficient conclusions on its role in a population of young healthy individuals.

The aim of this study is to determine relationships between the traditional cardiovascular risk factors included in the SCORE system and cardiovascular risk estimated with the SCORE system, IMT and FMD in a low risk population.

Methods

One hundred and nineteen patients (60 women, 59 men) aged between 25 and 50, with no known cardiovascular disease and a SCORE system-estimated risk < 5%, were included in our study.

The average age between the subpopulations of men and women were comparable (mean + SD): 38.9 ± 5.5 *vs*. 38.8 ± 6.0 age ($p = 0.96$).

The exclusion criteria included any somatic (i.e. hypothyroidism, Cushing disease, diabetes, impaired glucose tolerance, systemic hypertension, metabolic syndrome) or mental diseases, pharmacotherapy (including contraception), changes in body weight during the three months preceding the start of the study, ovariectomy, pregnancy, menopause, significant hyperlipidemia (TCh ≥ 320 mg/dL, LDL-Ch ≥ 240 mg/dL), and severe arterial hypertension (≥ 180/110 mm Hg).

The study was approved by the local Ethics Committee, and all patients gave written informed consent prior to enrollment.

The clinical characteristics of the patients included: medical history, physical examination (arterial pressure, body mass index, and waist/hip ratio), laboratory tests (mainly lipidograms, fasting glucose), accessory investigations (electrocardiogram, echocardiography), and detailed characteristics of therapy used.

The subjects were instructed to fast overnight and avoid smoking for 24 hours prior to the examination.

Based on the SCORE system tables by the Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice [2], ten-year risk of cardiovascular death (for current age and extrapolated for age of 60) was evaluated for each individual. Lipid parameters (serum cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) and fasting glucose were obtained immediately by the routine laboratory.

The following vascular ultrasonography techniques [5, 6] were used to assess the functional and structural remodeling of the vascular system: FMD, IMT and nitroglycerin mediated dilatation (NMD).

Flow-mediated dilatation

The measurements of brachial artery FMD were done in a quiet, temperature-controlled room, between 9 and 11 am. Patients were examined after at least a ten minute rest; ultrasound examination was performed in a supine position.

Expert investigators took measurements in a B-mode presentation using a high frequency ultrasound system (Philips HDI 4000) equipped with a vascular software for two-dimensional (2D) imaging, color and spectral Doppler, an internal electrocardiogram monitor and a high frequency vascular transducer (multiple-frequency: 7–10 MHz).

The brachial artery of the dominant forearm was visualized above the antecubital fossa in a longitudinal plane, with a sphygmomanometric cuff on the proximal portion of the arm. The brachial artery diameter (BAd) was described as a minimal distance between 'm' lines, from the anterior to posterior wall of the artery. Images were acquired with electrocardiography gating; with measurements made in end diastole, which corresponds to the onset of the R wave.

The study was performed in three stages:

— stage 1: baseline BAd and flow measurements were made, and the average was calculated for each subject;

Table 1. Clinical characteristics.

	Mean	SD	Minimum	Maximum
Age	38.8	5.7	27	50
Systolic blood pressure [mm Hg]	119.8	15.5	90	160
Total cholesterol [mg/dl]	209.6	40.6	139	326
HDL cholesterol [mg/dL]	56.0	12.9	27	95
LDL cholesterol [mg/dL]	124.6	32.6	69	218
Triglicerides [mg/dL]	141.0	91.7	29	397
Glucose [mg/dL]	90.8	9.9	67	121

HDL — high density lipoprotein; LDL — low density lipoprotein

- stage 2: sphygmomanometer cuff was inflated to 200 mm Hg to occlude arterial inflow for three minutes;
- stage 3: brachial artery diameter and blood flow were measured and the mean calculated of the values obtained 50–60 seconds after cuff deflation.

Considering these two measurements (baseline and after-cuff deflation), FMD was calculated (percentage increase of artery diameter compared to baseline results).

After a ten minute rest, a sublingual tablet of nitroglycerin (0.5 mg) was administered to determine the maximum obtainable exogenous vasodilatory response. Brachial artery diameter and blood flow were measured following NTG, and NMD was determined (NTG--induced percentage increase of the artery diameter).

To eliminate the influence of BAd morphology on FMD values, the FMD × BAd and FMD/NMD indices were assessed [6].

Intima media thickness

All measurements were performed in the common carotid arteries 1 to 2 cm proximally to the carotid bulb. The common carotids were studied in longitudinal planes with anterior and lateral approaches. IMT was measured on the posterior wall of the artery. An average of ten measurements was used to calculate IMT.

Statistical analysis

All analysis was performed using MedCalc 9.0. Statistical significance was set at $p < 0.05$. Continuous variables were described as mean, standard deviation, minimum and maximum. SCORE system was described as median, 25–75%, minimum and maximum. T-test was used to compare normally distributed continuous variables. In the case of abnormal distribution, the U Mann-Whitney test was used. Comparisons between subgroups of IMT, FMD, NMD, FMD × BAd, FMD/NMD classified on the basis of SCORE system were performed with one way analysis of variation (ANOVA). Spearman's rank correlation test was applied to assess relations between variables. Stepwise multiple regression was used to analyze the relationship between a dependent variable: IMT, FMD, NMD, FMD × BAd, FMD/NMD and independent variables.

Results

Clinical characteristics of the study group are presented in Table 1. None of the participants revealed serum fasting glucose above 126 mg/dL or triglycerides above 400 mg/dL.

All the vascular parameters are shown in Table 2.

The SCORE system parameters and IMT/ /FMD — multivariate regression analysis

We evaluated the association of the SCORE system parameters (age, sex, smoking, SBP, TCh concentration) and vascular parameters (IMT, FMD). IMT values were significantly correlated with the following: age, SBP, TCh and FMD (R-adjusted 0.45; $p < 0.001$). FMD values were significantly associated with sex and IMT (R-adjusted 0.24; $p < 0.001$). NMD values were significantly correlated with sex and IMT (R-adjusted 0.29; $p < 0.001$). Moreover, after inclusion of BAd, the only factor significantly correlating with FMD and NMD was BAd (R-adjusted 0.31; $p < 0.001$; R-adjusted 0.44; $p < 0.001$). The FMD × BAd index and FMD/NMD ratio were significantly influenced by IMT (R-adjusted 0.04; $p = 0.015$; R-adjusted 0.04; $p = 0.02$). All the results are presented in Table 3.

The SCORE system

The SCORE-estimated risk for the study population was relatively low: 0 to 4% (median-1, 25–

Table 2. Intima media thickness, brachial artery diameter (BAd), flow mediated dilatation (FMD), nitroglycerin mediated dilatation (NMD), FMD × BAd index, FMD/NMD index in the group examined.

	Mean	SD	Minimum	Maximum
Intima media thickness [mm]	0.52	0.08	0.37	0.78
Brachial artery diameter [mm]	3.51	0.69	2.4	5.07
Flow mediated dilatation [%]	17.5	7.8	0.73	41.8
Nitroglycerin mediated dilatation (%)	27.0	9.0	8.4	51.0
FMD × BAd	58.2	22.4	3.0	116.0
FMD/NMD	0.64	0.19	0.04	1.06

Table 3. Multiple regressions of dependents: intima media thickness (IMT), flow mediated dilatation (FMD), nitroglycerin mediated dilatation (NMD), FMD × BAd index, FMD/NMD index.

Independent variables	Coefficient	Std. error	p
Multiple regression of dependent IMT (Constant 0.1037; R-adjusted 0.45; p < 0.001)			
Age	0.0044	0.00097	< 0.0001
SBP	0.0018	0.00039	< 0.0001
TCh	0.0003	0.00014	0.03
FMD	–0.0021	0.00075	0.006
Multiple regression of dependent FMD (Constant 39.89; R-adjusted 0.31; p < 0.001)			
BAd	–6.4	0.86	< 0.0001
Multiple regression of dependent NMD (Constant 57.56; R-adjusted 0.44; p < 0.001)			
BAd	–8.71	0.91	< 0.0001
Multiple regression of dependent FMD × BAd (Constant 89.62; R-adjusted 0.04; p = 0.02)			
IMT	–60.26	1.63	0.0059
Multiple regression of dependent FMD/NMD (Constant 0.92; R-adjusted 0.04; p = 0.015)			
IMT	–0.53	0.22	0.015

BAd — brachial artery diameter; SBP — systolic blood pressure; TCh — total cholesterol

–75 Q: 0–2). The risk was higher for men than for women (1% *vs*. 0%, p < 0.0001). Furthermore, cardiovascular risk extrapolated for the age of 60 was as follows: median 4, 25–75 Q: 2–7 (Fig. 1).

Further analysis revealed a significant association between a ten year risk of cardiovascular death based on the SCORE system and IMT (ANOVA p < 0.001; Fig. 2), FMD (ANOVA p < 0.001; Fig. 3), NMD (ANOVA p < 0.001) and FMD × BAd index (ANOVA p = 0.017; Fig. 4), which therefore matches to the SCORE system in terms of low risk range. However, no relationship has been observed between FMD/ /NMD ratio and SCORE-risk (ANOVA p = 0.272).

There was a significant relationship between extrapolated SCORE-risk and IMT (r = 0.55; p < 0.0001), FMD (r = –0.46; p < 0.0001), NMD (r = –0.49; p < 0.0001), FMD × BAd index (r = 0.208; p = 0.024). But no association was found in terms of FMD/NMD ratio (r = –0.13; p = 0.16). The difference between the correlation for FMD and FMD × BAd index was statistically significant (p = 0.0293).

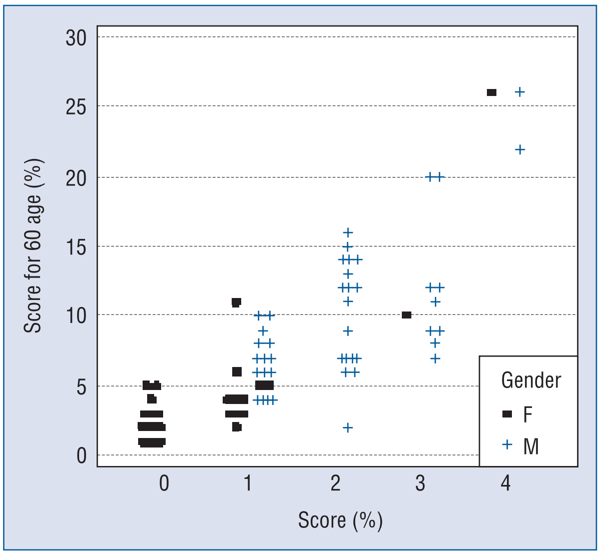

Figure 1. Actual, and extrapolated to the age of 60, cardiovascular risk estimated by use of SCORE system in the males and females examined.

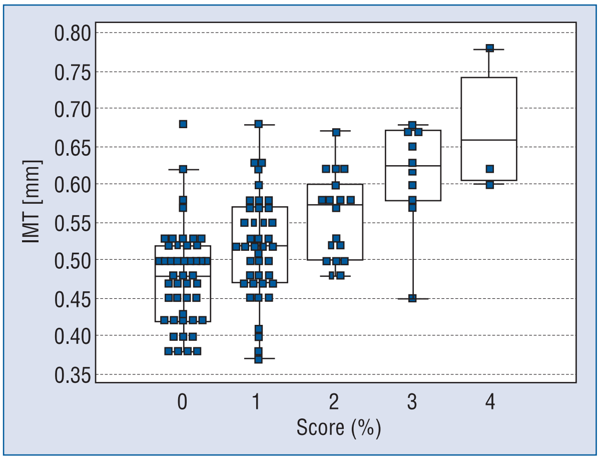

Figure 2. Intima media thickness (IMT) and the SCORE risk.

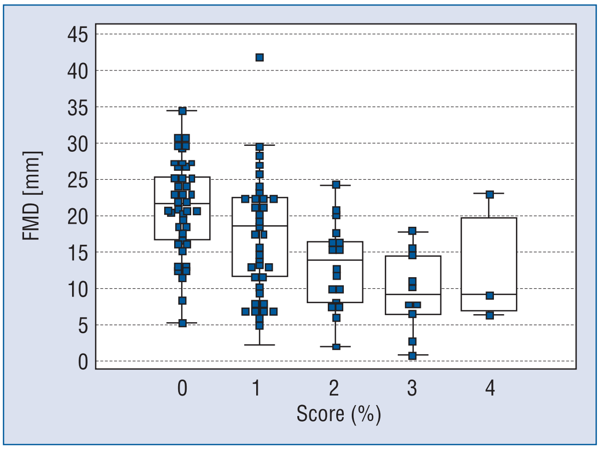

Figure 3. Flow mediated dilatation (FMD) and the SCORE risk.

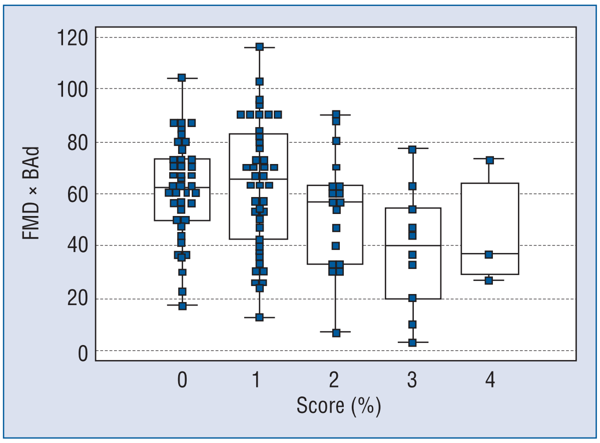

Figure 4. Flow mediated dilatation (FMD) × brachial artery diameter (BAd) index and the SCORE risk.

Discussion

Our study evaluated a population of young, apparently healthy individuals of low ten-year risk of cardiovascular death.

Multivariate regression analysis demonstrated close associations between IMT and classical risk factors: age, SBP, TCh and FMD values, which is in line with previous observations [7–10]. The Kuopio Ischaemic Heart Disease Risk Factor Study of 1,165 men demonstrated that SBP constitutes an independent factor affecting intima-media complex thickening [7]. Sun et al. [8] provided similar observations of a population of 1,781 apparently clinically healthy individuals. Moreover, IMT has been showed to correlate with TCh, HDL-Ch, LDL-Ch and triglicerides serum concentrations [9, 10].

Our observation showed a significant inverse correlation between IMT and FMD that was consistent with the literature data [11–13]. IMT correlated with FMD in patients without macroscopic anatomical atherosclerotic lesions. Atherosclerotic plaques or substantial IM complex thickening diminishes vessel relaxing properties, probably in a non-linear relation. But vascular parameters reflect different stages of atherogenesis: IMT corresponds with large arteries' remodeling, which starts early but is predominantly found in elderly patients, whereas FMD reflects endothelial function.

Reliable interpretation of FMD-dependent regression analysis is more complex. A regression multifactorial model showed that BAd might affect up to 31% of FMD values. This was in line with our previously published data [14]. Making the measure of FMD independent from BAd by introducing the FMD × BAd index, the independent factor influencing the value of the index was IMT. However, IMT affected only 4% of obtained values.

Similarly to FMD, NMD values were mainly dependent on BAd. Nonetheless, FMD/NMD ratio, which is an indirect index of vasorelaxing vascular properties independent of artery stiffness, revealed an association only with IMT. Our observations concerning FMD × BAd and FMD/NMD indices require further examination.

The estimated ten-year risk of cardiovascular death in our population was relatively low: 0 to 1% for up to 74% of participants. Nevertheless, even in the population of such low cardiovascular risk, a statistically significant association between the SCORE system and vascular parameters was found. Higher-risk individuals revealed thicker intima-media complex and decreased FMD. Therefore, the low risk population is heterogenous and even a difference by 1% in the SCORE risk (insignificant differences in the SCORE system score) was associated with substantial differences in vascular parameters.

Further analysis also showed a significant association of FMD × BAd index with the SCORE risk. However, as the SCORE system includes male sex (which is usually accompanied by a larger brachial artery diameter), the described association was not as strict as for FMD values.

To the best of our knowledge, our study is the first evaluation of the association between the SCORE system and vascular parameters. A similar observation has been confirmed for the Framingham scale. Witte et al. [15] revealed a close correlation between cardiovascular risk factors and FMD values in individuals with low risk according to the Framingham scale. The authors concluded that an increased risk of 1% is accompanied by decreased FMD values of 1.42%, but only in a population of low risk patients according to the Framingham scale. This was not related to higher risk patients [15].

Our results confirm beyond doubt a reliable association of a simple stratifying scale (the SCORE system) with indices of early vascular remodeling in a low risk population. Every increase by 1% in the SCORE risk corresponds with more advanced vascular abnormalities. It supports the clinical significance of the SCORE system. Moreover, it suggests that analysis of vascular indices may constitute an alternative method of risk stratification. Both the SCORE system and vascular parameters analysis, including FMD, IMT may be useful in identifying young, apparently healthy individuals requiring systematic check-ups and intensive lifestyle modification.

Conclusions

In a population of low cardiovascular risk, intima-media thickness is determined by classical risk factors included in the SCORE system. FMD values are closely dependent on the brachial artery diameter that in FMD assessment the artery diameter should be taken into account. Both FMD × × BAd index and FMD/NMD ratio have been showed to be related to IMT.

Young adults without clinically apparent cardiovascular diseases are characterized by low and sex-dependent risk according to SCORE. There are observed relationships between the SCORE risk and IMT and FMD values.

Acknowledgements

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