Simple exercise test score versus cardiac stress test for the prediction of coronary artery disease in patients with type 2 diabetes

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INTRODUCTION Type 2 diabetes markedly increases the risk of coronary heart disease (CHD), and screening for CHD is suggested by the guidelines.

OBJECTIVES The aim of the study was to compare the diagnostic usefulness of the simple exercise test score, incorporating the clinical data and cardiac stress test results, with the standard stress test in patients with type 2 diabetes.

PATIENTS AND METHODS A total of 62 consecutive patients (aged 65.4 ± 8.5 years; 32 men) with type 2 diabetes and clinical symptoms suggesting CHD underwent a stress test followed by coronary angiography. The simple score was calculated for all patients.

RESULTS Significant coronary stenosis was observed in 41 patients (66.1%). Stress test results were positive in 36 patients (58.1%). The mean simple score was high (65.5 ± 14.3 points). A positive linear relationship was observed between the score and the prevalence of CHD ($R^2 = 0.19$; $P < 0.001$) as well as its severity ($R^2 = 0.23$; $P < 0.001$). The area under the receiver-operating characteristic curve for the simple score was 0.74 (95% confidence interval [CI], 0.62–0.86). At the original cut-off value of 60 points, the score had a similar prognostic value to that of the standard stress test. However, in a multivariate analysis, only the simple score (odds ratio [OR], 1.46; 95% CI, 1.11–1.94; $P < 0.01$ for an increase in the score by 1 point) and male sex (OR, 1.57; 95% CI, 1.24–1.98; $P < 0.001$) remained independent predictors of CHD.

CONCLUSIONS In patients with type 2 diabetes, the simple score correlated with the prevalence and severity of CHD. However, the cut-off value of 60 points was inadequate in the population of diabetic patients with high risk of CHD. The simple score used instead of or together with the stress test was a better predictor of CHD than the stress test alone.
duration of diabetes and treatment with oral hypoglycemic drug or insulin or both were recorded; other types of pharmacological treatment (antihypertensive and lipid-lowering drugs) were also considered. The hormonal status (pre- or postmenopausal period, estrogen replacement therapy) was recorded in women. The clinical status before the stress test was assessed, including heart rate and blood pressure.

Cardiac stress test Patients with any resting changes in the ST segment on ECG were excluded from the study. The standard Bruce protocol was used for the stress test with 12-lead ECG recorded during the test and in the recovery phase; ST-segment depression at 60 ms after the J point was estimated during peak exercise and in the recovery phase at 3-minute intervals. The horizontal or downsloping ST-segment depression of at least 1 mm was considered diagnostic for myocardial ischemia.

A positive stress test result for diagnosing myocardial ischemia comprised clinical symptoms (exertional angina) and/or ST-segment depression on ECG despite angina. The occurrence of typical angina requiring the termination of the test was accepted as a “clinically positive” test result. A negative result meant discontinuation of the test after achieving the heart rate (predefined for the patient’s age) without clinical and/or ECG signs of ischemia. To calculate the simple score, we classified pain as present during the stress test and either requiring or not requiring discontinuation of the test. The score was higher if pain was observed. The exercise test was performed 1 day before coronary angiography.

Calcium scoring, or cardiac magnetic resonance imaging, the cardiac stress test is still the most widely used approach in the diagnostic algorithm of CHD, also in diabetics. The usefulness of different diagnostic scores incorporating clinical data and traditional coronary risk factors (SCORE, Framingham Risk Score) as well as scores incorporating the parameters of the stress test (Duke score) has been confirmed. Morise et al. reported the prognostic significance of a simple exercise test score incorporating clinical data and stress test results, which exceeded the prognostic performance of the widely used Duke score.

The aim of our study was to investigate the diagnostic performance of the simple score used by Morise et al. in patients with type 2 diabetes and clinical suspicion of CHD.

Patients and Methods Consecutive patients with type 2 diabetes and clinical suspicion of CHD (exertional angina or equivalent: exertional or nocturnal dyspnea or impaired physical tolerance after exclusion of chronic heart failure), who were referred for coronary angiography to the Międzyleski Hospital in Warsaw, Poland, were considered eligible and were included into the study after providing informed consent. The local ethics committee approved the study.

At baseline, patients underwent a full clinical examination, laboratory analysis, standard 12-lead electrocardiography (ECG), echocardiography, and stress test followed by coronary angiography. Chest pain was assessed according to the Diamond’s classification (typical angina, atypical angina, non-anginal pain). Symptoms of heart failure, other diagnosed diseases (hypertension), and coronary risk factors were recorded. Duration of diabetes and treatment with oral hypoglycemic drug or insulin or both were recorded; other types of pharmacological treatment (antihypertensive and lipid-lowering drugs) were also considered. The hormonal status (pre- or postmenopausal period, estrogen replacement therapy) was recorded in women. The clinical status before the stress test was assessed, including heart rate and blood pressure.

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<table>
<thead>
<tr>
<th>TABLE 1 Simple exercise test score</th>
</tr>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>maximal heart rate, bpm</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>exercise ST-segment depression, mm</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>age, y</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>history of angina</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>diabetes</td>
</tr>
<tr>
<td>exercise test-induced angina</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>hypercholesterolemia</td>
</tr>
<tr>
<td>smoking</td>
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<tr>
<td>estrogen status</td>
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</tbody>
</table>
The study included 62 patients (aged 65.4 ±8.5 years; 32 men). The baseline characteristics of the studied population are presented in Table 2. The mean duration of diabetes was 6.2 ±4.1 years. Most patients were treated with oral hypoglycemic drugs (metformin, 48 patients; sulfonylureas, 27 patients; acarbose, 9 patients); 8 patients received long-acting insulin once daily. All patients with hyperlipidemia received statin treatment. More than half of the patients (51.6%) had multivessel disease. Significant coronary stenosis was more frequent in men than in women (84.4% vs. 46.6%; P <0.01). There were no other significant differences between men and women.

A positive stress test result (ST-segment depression or typical angina requiring discontinuation of the test) was observed in 36 patients (58.1%). Typical angina was present during the test in 23 patients (37.1%), and diagnostic ST-segment depression in 25 patients (40.3%). The stress test was not diagnostic in 2 patients. The simple score in the whole group ranged between 38 and 107 points and the mean value was 65.5 ±14.3 points. More than half of the patients (n = 39, 62.9%) had high risk of CHD according to the simple score and only 1 person had low risk.

Diagnostic value of the cardiac stress test A positive stress test result was associated with significant coronary stenosis on angiography (P <0.01). The performance and accuracy of the stress test are presented in Figure 1. The sensitivity of the stress test was slightly higher in men than in women (84.4% vs. 46.6%).

Results Study population

TABLE 2 Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole group (n = 62)</th>
<th>Men (n = 32)</th>
<th>Women (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, y</td>
<td>65.4 ±8.5</td>
<td>64.9 ±10.1</td>
<td>66.0 ±6.6</td>
</tr>
<tr>
<td>risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>arterial hypertension</td>
<td>80.6</td>
<td>84.4</td>
<td>76.6</td>
</tr>
<tr>
<td>hypercholesterolemia</td>
<td>54.8</td>
<td>59.4</td>
<td>50.0</td>
</tr>
<tr>
<td>smoking</td>
<td>56.5</td>
<td>65.6</td>
<td>46.6</td>
</tr>
<tr>
<td>obesity</td>
<td>54.8</td>
<td>56.3</td>
<td>53.3</td>
</tr>
<tr>
<td>diabetes duration, y</td>
<td>6.2 ±4.1</td>
<td>6.8 ±4.2</td>
<td>5.6 ±3.8</td>
</tr>
<tr>
<td>clinical symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>typical angina</td>
<td>38.7</td>
<td>43.8</td>
<td>33.3</td>
</tr>
<tr>
<td>atypical angina</td>
<td>21.0</td>
<td>18.8</td>
<td>23.3</td>
</tr>
<tr>
<td>noncardiac pain</td>
<td>21.0</td>
<td>15.6</td>
<td>26.6</td>
</tr>
<tr>
<td>others</td>
<td>19.4</td>
<td>21.9</td>
<td>16.6</td>
</tr>
<tr>
<td>coronary angiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>4.8</td>
<td>0</td>
<td>10.0</td>
</tr>
<tr>
<td>lesions &lt;50%</td>
<td>29.0</td>
<td>15.6</td>
<td>43.3</td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>14.5</td>
<td>25.0</td>
<td>3.3</td>
</tr>
<tr>
<td>multivessel disease</td>
<td>51.6</td>
<td>59.4</td>
<td>43.3</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or percentage.

Simple exercise test score The simple score was calculated according to Morise et al.15,19 (Table 1). In all patients, the score included age, history of angina, diagnosis of diabetes, and the following exercise test parameters: maximal heart rate, extent of ST-segment depression, and angina during the test. In women, the estrogen status was also estimated assuming the presence of regular menstruations or use of estrogen replacement therapy as positive. Tobacco smoking in women and hypercholesterolemia in men was also included. Based on the score, patients were divided into 3 groups of low (0–39 points), moderate (40–60 points), and high risk (>60 points).19,20

Coronary angiography All patients underwent coronary angiography. The presence of 50% stenosis or more in 1 or more large coronary arteries was considered as confirmed diagnosis of CHD. Based on the severity, CHD was divided into 4 categories: 1 – normal angiography; 2 – nonsignificant lesions (up to 50%); 3 – significant stenosis in 1 coronary artery (≥50% or more); 4 – multivessel disease (≥50% stenosis in at least 2 coronary arteries).

Statistical analysis We analyzed the diagnostic value of the simple score in comparison with the standard stress test for the prediction of significant angiographic CHD in the diabetic cohort. We assessed sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values of both tests. We also calculated positive and negative likelihood ratios for both tests. Moreover, we estimated the discriminative power of the threshold value for high score originally proposed by Morise et al.15,19. To estimate and verify the optimal threshold value for the simple score in our diabetic population, a receiver-operating characteristic (ROC) curve was plotted.

To estimate the significance of the differences between the groups, the t test was used for continuous variables with normal distribution and the nonparametric test for those with nonnormal distribution. Correlations between the noninvasive tests and coronary angiography results were examined using the V test. In a multivariate analysis, the general discriminant analysis was used. Parameters that differed significantly in a univariate analysis and those with a P value of less than 0.1 were included in the general discriminant analysis. A model was constructed for the prediction of CHD. For all calculations, STATISTICA v. 9.0 was used (StatSoft, Tulsa, Oklahoma, United States). A P value of less than 0.05 was considered statistically significant.
(angina) had relatively low sensitivity in men (42.3%) and women (61.5%) with better specificity in women (87.5%) than in men (60.0%). Despite low sensitivity of exertional anginal pain, its positive predictive value was high (82.6%) but negative predictive value was low (54.1%), especially among women (26.3%). The positive likelihood ratio for the clinical component was 2.56 in the whole study population, but it was significantly higher in women (4.92). The ECG component of the test also had relatively low sensitivity (whole group, 53.8%; men, 61.5%; women, 38.5%) and low negative predictive value (51.4%), but its specificity was high both in men (80.0%) and women (81.3%). The positive likelihood ratio was 2.83 in the whole population and was higher in men (3.08).

Silent ischemia during the stress test (13 patients) predicted significant disease on coronary angiography. The ischemia was not a very sensitive predictor of CHD but it was highly specific (>85%), especially in men (100%). Low sensitivity of silent ischemia resulted in its relatively low diagnostic accuracy (below 50%).

**Diagnostic value of the simple exercise test score**

The mean value of the simple score was high in our cohort (65.5 ±14.3 points) and did not vary significantly between men and women. The mean value was significantly higher in the group with CHD confirmed by angiography compared with the remaining group (69.5 vs. 57.7; P <0.01). There was a steady increase in the prevalence of CHD as the score increased (r = 0.44; R² = 0.19; P <0.001; [FIGURE 2](#)), and the score was positively correlated with the severity of coronary lesions assessed by the semiquantitative method (r = 0.48; R² = 0.23; P <0.001).

A predefined cut-off value of 60 points was not a good predictor of significant lesions on coronary angiography. In the whole group and the subgroups of men and women, the diagnostic accuracy of the simple score (by the cut-off value of 60 points) was not significantly better than the stress test result ([FIGURE 1](#)). Sensitivity of the score was higher in women than in men but its specificity was much lower in women compared with men ([FIGURE 1](#)). The positive likelihood ratio for the score was significantly higher in men than in women (3.33 vs. 1.06). The area under the ROC curve (AUC) for the score was 0.74 for the whole group (95% confidence interval [CI], 0.62–0.86) and was generally similar between men and women. A suggested cut-off value for the simple score in our cohort was 48 points, which was lower than the predefined cut-off value of 60 points.

In a univariate analysis, patients with confirmed CHD differed significantly from those without the disease in terms of the higher percentage of men, more frequent positive stress test result (clinically or based on the ECG criteria or both), and higher mean value of the simple score. Other characteristics such as age, maximum workload achieved (in metabolic equivalents), presence

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**FIGURE 1** Performance and accuracy of the cardiac stress test and simple exercise test score for the prediction of significant coronary stenosis

Abbreviations: NPV – negative predictive value, PPV – positive predictive value
of silent ischemia or the simple score exceeding 60 points were not significantly different between those groups. In a multivariate analysis, only male sex (odds ratio [OR], 1.57; 95% CI, 1.24–1.98; \( P < 0.001 \)) and the simple score expressed as continuous variables (OR, 1.46; 95% CI, 1.11–1.94; \( P < 0.01 \) for an increase in the score by 1 point) remained independent predictors of CHD on angiography. The model with the best discriminative power included the following variables: male sex, age, and the simple score. The discriminative power of that model was slightly higher than that of the model including male sex, age, and stress test result and was comparable to the model including male sex, age, stress test result, and the simple score (TABLE 3).

**DISCUSSION**  
Diabetes is a strong coronary risk factor, and the optimal diagnostic algorithm for risk assessment in this disease has not been designed so far.\(^2,21–23\) Despite rapid development of new imaging methods for diagnosing CHD, the cardiac stress test is still the most widely used option.\(^23\) However, its diagnostic value in diabetic patients is limited for many reasons such as lack of typical clinical symptoms manifesting during the stress test as silent ischemia.\(^25\) On the other hand, exercise-induced ST-segment depression is considered to result from significant narrowing of the large epicardial coronary artery, but it also might result from changes in the smaller arteries as well as disturbed microcirculation in diabetes.\(^26\)

According to the standard stress test protocol, the primary diagnostic index is exercise-induced ST-segment deviation on ECG.\(^17,18,24\) The diagnostic power of the stress test is increased if clinical symptoms of exercise-induced ischemia are also taken into account; exertional angina is the most important clinical symptom of a positive test result.\(^16,17,19\) Many other clinical parameters are also considered mostly for prognostic reasons.\(^21\) An important simple prognostic sign investigated in the population of diabetic patients is maximum workload achieved in the stress test.\(^27\)

Fearon et al.\(^28\) compared several more complex diagnostic scores derived from the stress test and including other factors such as age, sex, clinical symptoms (history of angina), coronary risk factors, maximum heart rate achieved, extent of ST-segment changes, presence of angina during the test (Duke score, Detrano score, Morise, and VA scores). Each score was compared with the diagnostic value of exertional ST-segment depression in the stress test alone. The diagnostic accuracy for each diagnostic score measured as the AUC was 0.73, 0.76, 0.77, and 0.78, respectively, and it was better than the diagnostic accuracy of ST-segment analysis alone (AUC, 0.67; \( z \)-score >1.96).

In our study, we used the exercise score originally proposed by Raxwal et al.,\(^19\) Froelicher et al.,\(^17\) and Morise et al.\(^15,28\) Raxwal et al.\(^19\) demonstrated an unequivocal advantage of the proposed exercise score over standard ST-segment assessment during the stress test (AUC, 0.79 and 0.67, respectively; \( P < 0.001 \)).\(^19\) Morise et al.\(^15\) used the exercise score for the assessment of mortality risk in the group of 4500 patients undergoing the stress test.\(^15\) The authors demonstrated a better prognostic value of the score compared with the most widely used Duke score for the prediction of death from any cause. In the study by Morise et al.,\(^15\) there were 514 diabetic patients (13%). The discriminative power of the Morise score for the prediction of death was slightly lower
in this subgroup compared with the nondiabetic population.

We applied the simple score to test its diagnostic value in diabetic patients referred for coronary angiography owing to clinical suspicion of CHD. Our population was well-balanced in terms of sex distribution. The average age was 65 years and average duration of diabetes was 6 years. All patients had diabetes and at least 1 additional coronary risk factor, which translated into a high risk of CHD. Coronary angiography revealed significant coronary lesions in 64.1% of the group; most of the patients had multivessel disease. High risk of CHD was also confirmed by a high mean value of the score (65.5 points) and a large proportion of patients at high risk based on the estimated simple score (62.9%). One-third of the study group had moderate risk. Only 1 patient had low risk according to the score. Morise et al. reported different results. In their study, the mean score was 33 points in the whole study group and 45 in the subgroup of diabetic patients. The percentage of high-risk patients was 16% and of the low-risk 37%.

The stress test result was positive in 58.1% of the patients in our study group. Most of the patients presented diagnostic ST-segment depression on ECG. The parameters of the diagnostic performance of the stress test were similar to the reference values. Clinical symptoms diagnostic for ischemia during the stress test had low diagnostic sensitivity as expected for patients with diabetes. Of note, sensitivity, positive predictive value, and positive likelihood ratio were much higher for women than for men. ST-segment depression on ECG had moderate sensitivity in the whole group, and it was clearly lower among women than among men. As for specificity for ischemia diagnosis, it was high both among men and women (>80%).

To evaluate the diagnostic performance of the simple score, we used the cut-off value of >60 points for the high-risk group, as originally proposed by Morise et al. The discriminatory power of this cut-off value was not better than the positive result of the standard stress test. The analysis of the simple score as a continuous variable showed its usefulness for prediction of CHD in patients with type 2 diabetes. The AUC was 0.74, which is in line with the results reported by Saxwal et al. (0.79) and Fearon et al. In our study, there was no significant difference in the AUC between men and women. Saxwal et al. examined only men, while Morise et al. reported a slightly better prognostic value in men than in women.

The result of the simple score correlated with the prevalence and severity of CHD on angiography. The ROC analysis showed that the cut-off value of 48 points was better for discrimination of patients with significant coronary lesions. However, we were unable to establish this precisely for the population with high pretest probability of CHD and a small number of low-risk patients. A multivariate analysis showed that the best model for CHD prediction in our population included age, sex, and the simple score. The discriminatory power of this model was slightly better than that based on the positive stress test result. This probably resulted from the fact that we applied the test in high-risk patients. According to the Bayes theorem and generally accepted conduct, the stress test should be used for the diagnostic purpose in the population with a moderate risk of the disease. Therefore, its discriminatory power for the prediction of CHD was limited in the high-risk population of diabetics with rather typical clinical symptoms of CHD. The use of the simple score EDS increased the discriminatory diagnostic power of the stress test in our population.

### Study limitations
The main limitation of the study is a relatively small number of patients. Data were collected from a single, relatively small center. Despite that, we were not able to find similar data and decided to publish our material as a pilot study. Our population was well-balanced in terms of the men-to-women ratio. In a post-hoc analysis, the main limitation was the high pretest probability of CHD derived from rather typical clinical symptoms, presence of coronary risk factors, mean age, and duration of diabetes. A high risk of the disease at baseline might have negatively affected the evaluation of the diagnostic performance of the stress test.

### Conclusions
We confirmed a correlation between the simple exercise test score and the prevalence and severity of CHD in patients with type 2 diabetes. However, the original cut-off value of 60 points was not adequate in our high-risk population. The stress test is still useful before referring diabetic patients for coronary angiography. For positive prediction of coronary lesions, the clinical component of the test had higher value in women and the ECG component in men. As for the simple score (as a continuous variable), its

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### TABLE 3 Comparison of 3 diagnostic models for the prediction of coronary heart disease in a multivariate analysis

<table>
<thead>
<tr>
<th>Patients with correct diagnosis, %</th>
<th>Wilks' lambda</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>negative</td>
</tr>
<tr>
<td>male sex, age, simple score</td>
<td>81.0</td>
</tr>
<tr>
<td>male sex, age, stress test result</td>
<td>61.9</td>
</tr>
<tr>
<td>male sex, age, stress test result, simple score</td>
<td>71.4</td>
</tr>
</tbody>
</table>

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use instead of the stress test alone or in combination with the test allows to better identify patients with diabetes with and without significant coronary stenosis.

REFERENCES

ARTYKUŁ ORYGINALNY

Prosta skala punktowa w porównaniu ze standardowym testem wysiłkowym w przewidywaniu choroby wieńcowej u chorych na cukrzycę typu 2

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SŁOWA KLUCZOWE
choroba wieńcowa, cukrzyca typu 2, ocena ryzyka, test wysiłkowy na bieżni, wartość predykcyjna testów

STRESZCZENIE

Wprowadzenie Cukrzyca typu 2 zdecydowanie zwiększa ryzyko choroby niedokrwiennej serca (coronary heart disease – CHD), dlatego wytyczne sugerują badania przesiewowe w kierunku CHD.

Celem badania było porównanie przydatności diagnostycznej prostej skali punktowej (simple exercise test score – SETS), łączącej dane kliniczne i wyniki testu wysiłkowego na bieżni, z przydatnością diagnostyczną standardowego testu wysiłkowego w grupie chorych z cukrzycą typu 2.

PacjenCi i metody U 62 kolejnych pacjentów (w wieku 65,4 ±8,5 roku; 32 mężczyzn) z cukrzycą typu 2 i objawami sugerującymi CHD wykonano test wysiłkowy, a następnie koronarografię. U wszystkich pacjentów dokonano pomiarów SETS.

Wyniki U 41 pacjentów (66,1%) stwierdzono obecność istotnych zwężen w naczyniach wieńcowych. Wynik testu wysiłkowego był dodatni u 36 pacjentów (58,1%). Średnia wartość SETS była wysoka (65,5 ±14,3 pkt). Dodatnią liniową zależność zaobserwowano między SETS a częstością występowania choroby wieńcowej (R² = 0,19; p <0,001) oraz jej ciężkością (R² = 0,23; p <0,001). Pole pod krzywą ROC dla skali punktowej wynosiło 0,74 (95% przedział ufności [CI] 0,62–0,86). Przy pierwotnie używanym punkcie odcięcia (60 pkt) SETS nie była lepsza niż standardowy test wysiłkowy. Jednak w analizie wieloczynnikowej tylko SETS (iloraz szans [OR] 1,46; 95% CI 1,11–1,94; p <0,01 dla wzrostu SETS o 1 pkt) i płeć męska (OR 1,57; 95% CI 1,24–1,98; p <0,001) pozostawały niezależnymi predyktorami CHD.

Wnioski U pacjentów z cukrzycą typu 2 SETS korelowały z częstością występowania i ciężkością CHD. Jednak punkt odcięcia na poziomie 60 pkt nie był odpowiedni dla populacji pacjentów z cukrzycą i wysokim ryzykiem CHD. Obliczenie wartości SETS zamiast wykonania testu wysiłkowego lub razem z wynikiem testu pozwalało lepiej przewidzieć CHD niż sam test wysiłkowy.