ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Association between fractional flow reserve and Duke treadmill score in patients with single-vessel disease

Süleyman Kalaycı[1], Belma Kalaycı[2], Ekrem Şahan[3], Asiye Ayça Ayyılmaz Boyacı[4]

[1]Ankara Training and Research Hospital, Ankara, Turkey
[2]Bülent Ecevit University, Faculty of Medicine, Zonguldak, Turkey
[3]Atatürk Chest Disease and Thoracic Surgery Research Hospital, Ankara, Turkey
[4]Türkiye Yüksek İhtisas Training and Research Hospital, Ankara, Turkey

Abstract

Background: Duke treadmill score (DTS) is an index that provides prognostic information calculated at exercise stress test. Fractional flow reserve (FFR) is an invasive method used to evaluate intermediate coronary stenosis. The direct relation of DTS and FFR has not been studied to date.

Aim: The present study aims to investigate the relationship between the DTS and FFR.

Methods: The study population consisted of a total of 106 patients with single-vessel disease, as confirmed by coronary angiography performed following EST, and whose FFRs were measured. The patients were separated into three groups according to the DTS values: low risk (DTS ≥ +5), intermediate risk (–10 ≤ DTS ≤ +4), and high risk (DTS ≤ –11). According to the FFR values, the patients were separated into two groups: FFR < 0.80 and FFR ≥ 0.80.

Results: Angina symptoms and chronic heart failure were more frequent in the group with FFR < 0.80 than the group with FFR ≥ 0.80; respectively, 95% vs. 69.8%, p = 0.020 and 15% vs. 3.5%, p = 0.045. The mean DTS value was lower in the group with FFR < 0.80 than the group with FFR ≥ 0.80 (1.60 vs. 5.07; p = 0.011). However, there were no statistically significant differences in the DTS risk groups among the FFR groups (p = 0.070). A weak positive correlation was found between the numerical DTS and FFR values (r = 0.139; p = 0.156). When the patients with high-risk were excluded, a statistically significant relationship was determined between the FFR and in the groups with low- and intermediate-risk in terms of the DTS values (p = 0.029).

Conclusion: In conclusion, our study results showed an association with FFR and in the groups with low and intermediate risk in terms of the DTS values. DTS levels can be useful to determine patients who require invasive management.

Key words: coronary artery disease, Duke treadmill score, fractional flow reserve

Kardiol Pol 2017; 75, 9: 877–883

INTRODUCTION

The identification of coronary artery disease (CAD) may sometimes be challenging, despite the availability of a great number of tests in this field. One of the non-invasive visualisation methods must be chosen in patients with a moderate pretest probability for CAD. Exercise stress testing (EST) is a non-interventional and affordable method commonly used in the evaluation of patients with suspected CAD [1]. In addition, EST may be used to evaluate the prognosis of CAD and functional capacity, and even provide guidance to other imaging modalities [2].

The Duke treadmill score (DTS) is a well-defined prognostic indicator used in the interpretation of data related to the EST, and its close relationship with mortality has been shown in many studies [1, 3]. DTS may be used to assess prognosis in patients with a moderate- or high-risk and to refer these patients to coronary angiography (CAG) [4, 5].

Fractional flow reserve (FFR) can be measured for each lesion in patients with a moderate coronary stenosis. This invasive method is used to determine haemodynamically important stenosis [6]. When the FFR is measured as < 0.80, the coronary lesion can be suggested to be haemodynami-

Address for correspondence:
Dr. Süleyman Kalaycı, Ankara Training and Research Hospital, Ankara, Turkey, e-mail: dr_suleyman_kalayci@yahoo.com
Received: 02.02.2017 **Accepted:** 11.04.2017 **Available as AoP:** 10.05.2017

cally important [7]. In the Fractional flow reserve versus Angiography for Multivessel Evaluation 2 (FAME-2) trial, the percutaneous coronary interventions (PCI) performed in the patients with stable angina under the guidance of FFR were shown to decrease the frequency of urgent revascularisations, compared to medical treatment [8].

In a previous study, the maximal ST segment depression during peak exercise has been shown to be correlated with the measurements of pressure during FFR [9]. In this study, we aimed to investigate the direct relationship between the DTS and FFR.

METHODS

Study population

In this retrospective study, the medical records of a total of 653 patients who underwent FFR measurement were analysed. The patient records revealed that 184 of these patients underwent EST prior to the procedure. Major exclusion criteria were as follows: recent myocardial infarction, left main or coronary artery by-pass graft lesions, receiving FFR for more than one vessel, severe left ventricular hypertrophy, development of bundle branch block or ventricular dysrhythmia during effort, presence of a suboptimal EST, and unavailability of adequate data. Finally, a total of 106 patients (73 males, 33 females; mean age: 57.7 years; range 40–76 years) who had single-vessel disease and who had undergone FFR measurement were included in the study.

Written, informed consent was obtained from each patient before FFR procedure. The study protocol was approved by the local Ethics Committee.

Treadmill exercise test and DTS

All patients underwent symptom-limited exercise treadmill testing according to the standard Bruce protocol, using the Philips StressVue Exercise Stress Testing System (Philips Health Care, 3000 Minuteman Rd., Andover MA, USA). Rest standing heart rate, arterial blood pressure, and 12-lead electrocardiogram (ECGs) were recorded prior to exercise. During each stage of exercise, and even the recovery period, heart rate and blood pressure measurements were recorded. All patients were monitored with 12-lead ECGs throughout exercise testing (i.e. until the end of the recovery period). The treadmill angina index data was gathered from event records. Maximal ST-segment deviation was measured at J+80 ms point. Exercise was discontinued if hypotension limiting angina, malignant ventricular arrhythmias, and marked ST depression (> 2 mm) was reported.

The DTS was calculated by two experienced cardiologists as previously defined by Mark et al. [1, 3] using the following formula:

$$DTS = \text{exercise time} - (5 \times \text{ST deviation}) - (4 \times \text{angina index}).$$

The exercise angina was scored as follows: the treadmill angina index was 0 for no angina, 1 for non-limiting angina, and 2 for exercise-limiting angina.

The patients were classified as low-, intermediate-, or high-risk according to the scores (low-risk DTS ≥ +5, intermediate-risk –10 ≤ DTS ≤ +4, and high-risk DTS ≤ –11) [10].

FFR measurement

Coronary lesions were visually assessed by the operator on diagnostic CAG, and FFR was performed to evaluate intermediate coronary stenoses. A 7 French guiding catheter without side-hole and 0.014-inch pressure monitoring guidewire (PrimeWire, Volcano, San Diego, CA, USA) was used for FFR measurement. All patients were anticoagulated with weight-adjusted doses of heparin (100 IU/kg). After calibration, a pressure-wire introduced into the guiding catheter and advanced distally to the coronary stenosis. FFR was calculated as the ratio of the mean distal coronary pressure divided by the mean aortic pressure after achievement of maximal hyperaemia. Maximal hyperaemia was obtained using intracoronary adenosine. Incremental boli of adenosine (60–300 μg) were administered by the intracoronary route. FFR value of < 0.80 was considered haemodynamically significant. After guiding catheter and pressure-wire placement, 0.2 mg intracoronary isosorbide dinitrate was administered to avoid coronary spasm.

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to evaluate normally-distributed data. The assumption of homogeneity of variance was tested using Levene's test. Continuous variables with normal distribution were compared by the t-test for independent groups. The χ^2 test was used to compare the categorical variables. The non-parametric Mann-Whitney U-test was used for independent variables with abnormal distribution. Correlation analyses were performed using the Pearson's correlation test. A p value of less than 0.05 was considered statistically significant for all tests.

RESULTS

Clinical characteristics

This study included a total of 106 patients with single-vessel disease, who underwent EST and thereafter received FFR measurement. Patients were separated into two groups based on FFR values: FFR < 0.80 and FFR ≥ 0.80. Age and sex were similar between these groups (Table 1). There were no significant differences between groups with respect to risk factors for CAD, such as diabetes mellitus, hypertension, hyperlipidaemia, smoking habits, and family history (p > 0.05). The personal history of the patients among groups did not differ in terms of the acute myocardial infarction, coronary artery bypass grafting, and PCI (p > 0.05).

However, there was a significant difference in the chronic heart failure and history of typical angina between the groups. The definition of the heart failure was assessed as the presence of a left ventricular ejection fraction

Table 1. Basal demographic characteristics of the patients

Variables	FFR < 0.80 (n = 20)	FFR ≥ 0.80 (n = 86)	p
Male sex	16 (80%)	57 (66,3%)	0.233
Age [years]	56.2 ± 8.7	58.1 ± 8.1	0.368
Diabetes mellitus	6 (30%)	33 (38.4%)	0.484
Hypertension	15 (75%)	55 (64%)	0.347
Hyperlipidaemia	15 (75%)	70 (81.4%)	0.518
Smoking consumption	8 (40%)	26 (30.2%)	0.399
Family history	10 (50%)	26 (30.2%)	0.093
Previous AMI	3 (15%)	7 (8.1%)	0.344
CABG history	1 (5%)	2 (2.3%)	0.516
PCI history	7 (35%)	22 (25.6%)	0.395
CHF	3 (15%)	3 (3.5%)	0.045*
Chronic kidney disease:			0.193
Stage 1	7 (35%)	44 (51.2%)	
Stage 2	13 (65%)	42 (48.8%)	
Typical angina	19 (95%)	60 (69.8%)	0.020*

Data presented as mean ± standard deviation (range) or n (%) of patients; *statisticaly significant ($p < 0.05$); AMI — acute myocardial infarction; CABG — coronary artery bypass grafting; CHF — chronic heart failure; FFR — fractional flow reserve; PCI — percutaneous coronary intervention

Table 2. Clinical characteristics of the patients

Characteristic	FFR < 0.80 (n = 20)	FFR ≥ 0.80 (n = 86)	p
BMI [kg/m^2]	28.37 ± 4.74	28.64±4.40	0.807
eGFR [mL/min/1.73 m^2]	89.16 ± 23.63	90.79 ± 16.34	0.773
LVEF [%]*	60 (55. 60) [55]	60 (60. 60) [58]	0.201
DTS*	1 (–3.50, 7.25) [1.60]	6 (2.00, 8.00) [5.07]	0.011
Vessel:			0.788
LAD	18 (90%)	79 (91.9%)	
Others	2 (10%)	7 (8.1%)	
Lesion [%]	60 (60.70) [62]	50 (50.60) [53]	< 0.001
FFR	0.74 ± 0.03	0.87 ± 0.04	< 0.001
Adenosine [µg]	146.50 ± 57.97	175.35 ± 44.26	0.015

Data presented as mean ± standard deviation (range) or n (%) of patients. *Discrete variables were expressed as the median (interquartile range) [mean]. BMI — body mass index; DTS — Duke treadmill score; eGFR — estimated (calculated) glomerular filtration rate; FFR — fractional flow reserve; LVEF — left ventricular ejection fraction; LAD — left anterior descending artery

(LVEF) < 40% [11]. It was determined to be 15% in the group of heart failure with FFR < 0.80 and 3.5% in those with FFR ≥ 0.80 ($p = 0.045$). History of typical angina was at the rate of 95% in the group with a FFR < 0.80 and 69.8% in the group with a FFR ≥ 0.80 ($p = 0.020$). Baseline demographic and clinical characteristics of the patients are presented in Tables 1 and 2.

Patients were classified classically based on the chronic kidney disease (CKD) [12]. Only stage 1 and stage 2 CKD were present in the study population. There was no significant difference in the stage of CKD between the groups ($p = 0.193$).

Body mass index and LVEF values were also similar between groups; respectively, 28.37 ± 4.74 vs. 28.64 ± 4.40, $p = 0.807$ and 55% vs. 58%, $p = 0.201$.

FFR in each group

The vessel in which FFR measurement was performed was commonly the left anterior descending artery, and was similar between groups (a total of 97 patients; 90.0% vs. 91.9%; $p = 0.788$). The other vessels were determined to be right coronary artery (four patients), circumflex artery (four patients), and diagonal (one patient), respectively.

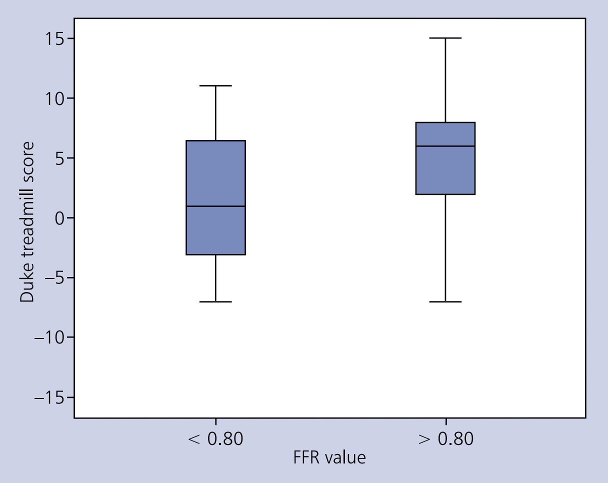

Figure 1. The handle-box graphic comparison of the mean Duke treadmill score and fractional flow reserve (FFR) values

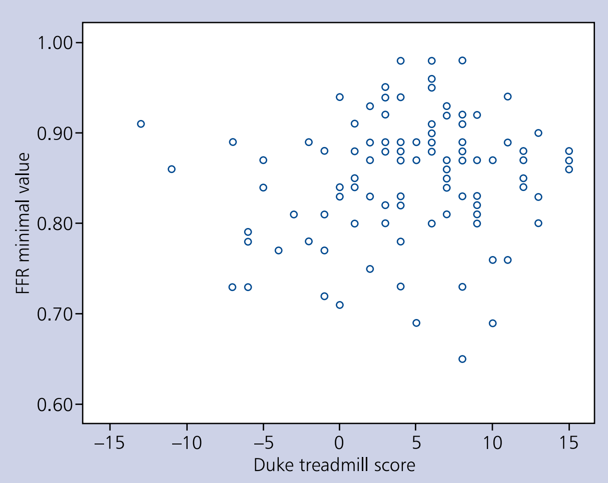

Figure 2. The dispersion graphic indicating the relationship between Duke treadmill score and fractional flow reserve (FFR) values

Table 3. Categorical analysis of the relationship between Duke treadmill score (DTS) and fractional flow reserve (FFR)

DTS category	FFR < 0.80 (n = 20)	FFR ≥ 0.80 (n = 86)	p
Low	6 (30%)	48 (55.8%)	0.070
Intermediate	14 (70%)	36 (41.9%)	
High	–	2 (2.3%)	

Data presented as n (%) of patients.

Table 4. Categorical analysis of the relationship between Duke treadmill score (DTS) and fractional flow reserve (FFR)

DTS category	FFR < 0.80 (n = 20)	FFR ≥ 0.80 (n = 84)	p
Low	6 (30%)	48 (57.1%)	0.029
Intermediate	14 (70%)	36 (42.9%)	

Data presented as n (%) of patients.

The degree of epicardial coronary stenosis was assessed visually by the operator carrying out the CAG, and a significant difference was present between the two groups (60% vs. 50%; p < 0.001). When the patients were evaluated altogether, the lesions measured for FFR at the highest frequency were determined to be the 50% stenoses (n = 42; 39.6%). While the mean value of FFR was 0.74 ± 0.03 in the group with a FFR < 0.80, it was 0.87 ± 0.04 in the group with FFR ≥ 0.80. (p < 0.001).

In addition, we found that a higher dose of adenosine was used to maintain maximal hyperaemia in the patients with FFR ≥ 0.80 during the FFR measurement (146.50 ± 57.97 vs. 175.35 ± 44.26; p = 0.015).

DTS in each group

The mean DTS value was significantly higher in the patients with FFR ≥ 0.80 than in the patients with FFR < 0.80 (5.07 vs. 1.60, p = 0.011). The median DTS values were 1.0 in the group with FFR < 0.80 and 6.0 in the patients with FFR ≥ 0.80 (Fig. 1).

The patients were separated into three categories according to the values of DTS, and they were evaluated according to the FFR values (Table 3). A statistically linear correlation could not be detected between DTS and FFR (r = 0.139, p = 0.156). When DTS was separated into three categories, there was no statistically significant difference between the groups (p = 0.070). The dispersion graphic (Fig. 2) and Pearson's correlation test were used to analyse a linear correlation between the DTS and FFR.

In addition, because an adequate number of patients did not fall into the high-risk group (DTS ≤ –11), the analysis was repeated by excluding this group. In the evaluation of the patients with low- and intermediate-risk according to the DTS, the proportion of patients with FFR < 0.80 was statistically significantly higher in the group with intermediate-risk compared with FFR ≥ 0.80 group (p = 0.029) (Table 4).

DISCUSSION

Duke treadmill score provides knowledge on the prognosis of CAD and is closely related to mortality [1, 3]. In previous studies; therefore, it has been compared with other non-invasive visualisation modalities or combinations [13–15]. In the study of Hachamovitch et al. [13], which included 2200 patients, single photon emission computed tomographic (SPECT) imaging with DTS increased the prognostic advantage. Another study of nuclear imaging reported that exercise myocardial perfusion scanning might be useful to assess the risk of cardiac arrest in patients included in the DTS intermediate-risk group [16].

Besides, Gibbsons et al. [17] performed a study to determine the long-term cardiovascular risks in patients included in the DTS intermediate-risk group who did not have perfusion defects in the myocardial perfusion imaging. In this study, cardiovascular survival rates were reported to be 99.8% at one year, 99.0% at five years, and 98.5% at seven years. The authors reported that these patients had low-risk for cardiac arrest, and they might be safely followed in the medical setting.

In another study, Marwick et al. [18] showed that cardiovascular mortality was lower in patients with normal stress echocardiogram, especially with intermediate-risk DTS.

Based on our findings, we can conclude that it may be reasonable to use additional visualisation methods to increase the diagnostic accuracy in the patients at intermediate-risk. The utilisation of an additional intervention is not recommended in patients with a low DTS and particularly in asymptomatic cases, and patients with a high DTS should be referred to CAG.

In a study evaluating the complexity of coronary lesions by DTS, the SYNTAX score and DTS were calculated in patients with a positive exercise test, who underwent CAG, and the relationship between these two parameters was assessed [19]. The results of this study revealed a strong negative correlation between the SYNTAX score and DTS.

There are a relatively small number of studies comparing DTS with the interventional methods, which evaluate CAD in functional terms. However, there are two studies that should be taken into consideration in this respect. Youn et al. [15] investigated the correlation between the DTS and coronary flow reserve (CFR), and found a strong correlation between DTS and CFR in individuals with microvascular angina. In the study of De Bruyne et al. [9], investigating the relationship between exercise stress test and FFR, measurements of pressure during FFR were found to be correlated with the maximal ST-segment depression during peak exercise.

In another study investigating the association between CFR and exercise capacity, DTS was found to be lower in the impaired CFR group than in the normal CFR group (–1.75 [–5.9, 5.0] vs. 7.5 [5.2, 9.41], $p < 0.001$) [20].

Duke treadmill score is a non-invasive, practical, and valuable method. Conversely, FFR is an interventional method, and has several disadvantages such as high cost and potential complications [21]. If there is a strong and linear correlation between the DTS and FFR, being informed about the patient's DTS and risk group prior to FFR measurement may prevent unnecessary measurements of FFR being carried out.

Fractional flow reserve assessment is a reliable hallmark of myocardial ischaemia because of its higher reproducibility of measurements and good correlation with both invasive and non-invasive tests [22]. However, the studies commonly included multi-vessel diseases such as in the FAME study. The FAME study showed that in patients with multi-vessel CAD, favourable outcome after routine measurement of FFR during PCI was obtained as compared with the standard strategy of PCI guided by angiography alone [23]. Chen et al. [22] demonstrated the reproducibility of FFR in patients with a single lesion. They found a significant correlation between quantitative coronary analysis and intravascular ultrasound parameters for FFR < 0.80 in a single lesion. Further large-scale randomised studies are warranted to confirm these results in patients with a single lesion.

In our study, the correlation analysis between the DTS and FFR did not reveal a strong correlation ($r = 0.139$). The possible reasons for this result may be the low number of patients included in the study and the presence of only two patients in the group with high DTS. Nearly all patients with a high pretest probability might not have undergone EST before the CAG. It may be the possible reasons of inadequate number of patients in the group with high-risk DTS. A total of 653 patients received FFR measurement in our clinic and only 184 (28%) underwent EST before the procedure. This finding supports the aforementioned interpretation.

Limitations of the study

There are some limitations of our study. A major limitation is the small sample size of the high-risk group according to DTS. Only two of the patients included in the study were in the group with high-risk DTS. When these patients were excluded from the analysis, a weak positive correlation was found between DTS and FFR. The preference of alternative visualisation methods rather than the EST in the evaluation of patients with high-risk or referring these patients directly to the CAG may be the reason for the presence of a small number of patients with high-risk. The presence of a strong relationship should be evaluated by conducting a large-scale study with a more homogeneous distribution.

Retrospective study design and intracoronary adenosine administration may also be limitations. In spite of the fact that intravenous adenosine is currently regarded as a "gold standard" method [24], intracoronary adenosine administration is widely used because of some advantages such as cost effectiveness, and simple and rapid application. As a consequence, IV adenosine administration might change the results when the FFR value approaches 0.80 (0.81 to 0.83) [25].

CONCLUSIONS

Consequently, we found an association between the DTS and the FFR values of patients on low and moderate DTS group. This result indicates that DTS levels may be helpful in guiding patient selection before interventional strategies. Further investigations in large-scale populations are required to determine a precise association between DTS and FFR to change daily practice.

Conflict of interest: *none declared*

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Cite this article as: Kalaycı S, Kalaycı B, Şahan E, Boyacı AAA. Association between fractional flow reserve and Duke treadmill score in patients with single-vessel disease. Kardiol Pol. 2017; 75(9): 877–883, doi: 10.5603/KP.a2017.0089.

Związek między cząstkową rezerwą przepływu a wskaźnikiem Duke w próbie wysiłkowej na bieżni u pacjentów z chorobą jednonaczyniową

Süleyman Kalaycı[1], Belma Kalaycı[2], Ekrem Şahan[3], Asiye Ayça Ayyılmaz Boyacı[4]

[1]Ankara Training and Research Hospital, Ankara, Turcja
[2]Bülent Ecevit University, Faculty of Medicine, Zonguldak, Turcja
[3]Atatürk Chest Disease and Thoracic Surgery Research Hospital, Ankara, Turcja
[4]Türkiye Yüksek İhtisas Training and Research Hospital, Ankara, Turcja

Streszczenie

Wstęp: Wskaźnik Duke w próbie wysiłkowej na bieżni (DTS) jest parametrem o wartości prognostycznej obliczanym w trakcie próby wysiłkowej. Pomiar cząstkowej rezerwy przepływu (FFR) stanowi inwazyjną metodę wykorzystywaną do oceny zwężenia tętnicy wieńcowej. Dotychczas nie przeprowadzono badania oceniającego bezpośrednią zależność między DTS a FFR.

Cel: Badanie przeprowadzono w celu oceny zależności między DTS a FFR.

Metody: Badana populacja liczyła 106 pacjentów z chorobą jednonaczyniową potwierdzoną w koronarografii wykonanej po próbie wysiłkowej, u których zmierzono również FFR. Uczestników badania podzielono na trzy grupy w zależności od wartości DTS: grupę niskiego ryzyka (DTS ≥ +5), grupę pośredniego ryzyka (–10 ≤ DTS ≤ +4) i grupę wysokiego ryzyka (DTS ≤ –11). Wyróżniono ponadto dwie grupy na podstawie wartości FFR: osoby z FFR < 0,80 i osoby z FFR ≥ 0,80.

Wyniki: Objawy dławicowe i przewlekła niewydolność serca występowały częściej w grupie z FFR < 0,80 niż u osób z wartościami FFR ≥ 0,80; odpowiednio 95% *vs.* 69,8%; p = 0,020 i 15% *vs.* 3,5%; p = 0,045. Średnia wartość DTS była niższa w grupie z FFR < 0,80 niż w grupie z FFR ≥ 0,80 (1,60 *vs.* 5,07; p = 0,011). Jednak nie stwierdzono statystycznie istotnych różnic pod względem grup ryzyka wg DTS między grupami wyróżnionymi na podstawie wartości FFR (p = 0,070). Odnotowano słabą dodatnią korelację między wartościami DTS a wartościami FFR (r = 0,139; p = 0,156). Po wykluczeniu pacjentów z grupy wysokiego ryzyka stwierdzono statystycznie istotny związek między wartościami FFR a grupami niskiego i pośredniego ryzyka wg wartości DTS (p = 0,029).

Wnioski: Podsumowując, wyniki uzyskane w niniejszym badaniu pokazały związek między FFR i grupami z niskim a pośrednim ryzykiem wg wartości DTS. DTS może być przydatny w identyfikowaniu pacjentów wymagających leczenia inwazyjnego.

Słowa kluczowe: choroba wieńcowa, wskaźnik Duke, cząstkowa rezerwa przepływu

Kardiol Pol 2017; 75, 9: 877–883

Adres do korespondencji:
Dr. Süleyman Kalaycı, Ankara Training and Research Hospital, Ankara, Turkey, e-mail: dr_suleyman_kalayci@yahoo.com

Praca wpłynęła: 02.02.2017 r. **Zaakceptowana do druku:** 11.04.2017 r. **Data publikacji AoP:** 10.05.2017 r.