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ARAŞTIRMA / RESEARCH

Use of CHA2DS2-VASc score in patients with stable angina pectoris with slow flow detected in coronary angiography

Koroner anjiyografide yavaş akım tespit edilen kararlı anjina pektorisli hastalarda CHA2DS2-VASc skorunun kullanımı

Cemal Köseoğlu[1], Çağrı Zorlu[1]

[1]Tokat Devlet Hastanesi, Kardiyoloji Kliniği, Tokat, Turkey

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Abstract

Purpose: Coronary slow flow (CSF) phenomenon is the slow movement of contrast to distal vascular structures during coronary angiography. Eventhough It has a high morbidity due to recurrent chest pain and different ischemic presentations, it is linked to coronary artery diseases (myocardial ischemia symptoms, life-threatening arrhythmias, recurrent acute coronary syndromes and sudden cardiac death). CHA2DS2-VASc score is a total of several risk factors for thromboembolism. Impaired renal function was shown to be a predictor of stroke and systemic embolism. We aimed to evaluate the CHA2DS2-VASc score to predict coronary slow flow.

Materials and Methods: Of the 3772 patients who applied to Tokat State Hospital with the diagnosis of stable angina pectoris (SAP) were screened retrospectively. A total of 71 patients with angiographically proven CSF and to meet the age characteristics of the CSF group, 84 patients who were completely normal coronary arteries (NCA) in the control group (n = 84) were screened and total of 155 patients were included in the study.

Results: Patients were classified into two groups: the CSF group (n=71) and the NCA group (n=84). When the characteristics of the CSF and control groups were compared, age, body mass index, systolic blood pressure, diastolic blood pressure, gender were similar. According to the results of the multivariate regression analysis, CHA2DS2-VASc score was an independent predictor (odds ratio: 1.872, 95 % CI: 0.849-1.981, p<0.001)

Conclusion: CHA2DS2-VASc score can be very useful in this regard as an easily applicable instrument. CHA2DS2-VASc score is independent indicators of CSF and can be used to predict CSF risk.

Keywords: Stabil angina pectoris, Coronary slow flow, CHA2DS2-VASc score

Öz

Amaç: Koroner anjiyografi sırasında kontrast maddenin distal vasküler yapılarının yavaş hareketine koroner yavaş akım (KYA) fenomeni denir. Tekrarlayan göğüs ağrısı ve farklı iskemik sunumlar nedeniyle yüksek morbiditeye sahip olmasına rağmen, koroner arter hastalığı (miyokardiyal iskemi semptomları, hayatı tehdit eden aritmiler, tekrarlayan akut koroner sendromlar ve ani kardiyak ölüm) ile ilişkilidir. CHA2DS2-VASc skoru, tromboembolizm için çeşitli risk faktörlerinden oluşan bir skorlama sistemidir. KYA' yı tahmin etmek için CHA2DS2-VASc skorunu değerlendirmeyi amaçladık.

Gereç ve Yöntem: Tokat Devlet Hastanesi'ne stabil angina pektoris (SAP) tanısı ile başvuran 3772 hasta geriye dönük olarak tarandı. Anjiyografik olarak kanıtlanmış KYA' sı olan 71 hasta ve kontrol grubu olarak da tamamen normal koroner anjiyografisi olan 84 hasta olmak üzere toplam 155 hasta çalışmaya dahil edildi.

Bulgular: Hastalar KYA grubu (n = 71) ve normal koroner arter grubu (n = 84) olmak üzere iki gruba ayrıldı. KYA ve kontrol gruplarının özellikleri karşılaştırıldığında yaş, vücut kitle indeksi, sistolik kan basıncı, diyastolik kan basıncı ve cinsiyet açısından aralarında istatiksel olarak anlamlı bir fark yok idi. Çok değişkenli regresyon analizi sonuçlarına göre, CHA2DS2-VASc skoru bağımsız bir belirleyiciydi (olasılık oranı [OR]: 1,872, % 95 CI: 0,849-1,981, p<0,001)

Sonuç: CHA2DS2-VASc skoru, kolay uygulanabilir bir araç olarak bu konuda çok yararlı olabilir. CHA2DS2-VASc skoru KYA' nın bağımsız göstergelerinden biri olabilir ve KYA riskini tahmin etmek için kullanılabilir.

Anahtar kelimeler: Stabil angina pektoris, Koroner yavaş akım, CHA2DS2-VASc skoru

Yazışma Adresi/Address for Correspondence: Dr. Cemal Köseoğlu, Tokat Devlet Hastanesi, Kardiyoloji Kliniği, Tokat, Turkey E-mail: drcemalkoseoglu@hotmail.com
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INTRODUCTION

The coronary slow flow (CSF) phenomenon is defined as the slow motion of the contrast agent distal to the coronary arteries in patients with abnormal or normal epicardial coronary arteries detected during coronary angiography (CAG)[1]. Although CSF causes recurrent chest pain and various ischemic symptoms, morbidity is high but mortality is not very high. This can be visiable in a single or more coronary arteries[1]. It is occur in 1% to 7% of patients who undergo coronary angiography, the only diagnostic method[2,3]. It most often affects young, male smokers[4] and is associated with coronary artery diseases (CAD) (myocardial ischemia symptoms, life-threatening arrhythmias, recurrent acute coronary syndromes and sudden cardiac death)[5,6]. Although no exact cause has been identified, endothelial dysfunction appears to have a common denominator of conditions such as diffuse atherosclerosis, systemic inflammation and microvascular disease. Many patients present to the hospital with complaints such as angina pectoris, shortness of breath or weakness in exertion. Therefore, multiple CAG procedures are applied to these patients. Sometimes it may even lead to ST elevation myocardial infarction[7]. Because of its relationship with fragmented QRS, which is considered an indication of sudden cardiac death and life-threatening arrhythmias, which are among the electrocardiographic findings[8], CSF has also been shown to be a potential indicator of sudden cardiac death[9].

CHA2DS2-VASc score is a scoring system consisting of risk factors indicating thromboembolism which is the main complication of atrial fibrillation. (AF)[10]. The present guidelines recommend the use of the CHA2DS2-VASc risk score in patients with AF to predict thromboembolic events[10]. Both CHADS2 and CHA2DS2-VASc scores have been shown to be associated with mortality in individuals with both stable coronary angina (SAP) and acute coronary syndrome (ACS) in the literatüre[8,9]. In a previous study, CHADS2 and CHA2DS2-VASc scores were used to estimate CAD severity[8]. In another population without AF, It has been reported that CHA2DS2-VASc scores predict mortality for adverse cardiovascular events and stroke and death risks in patients with Takotsubo syndrome[11] and patients with sinus syndrome after pacemaker implantation[12].

Considering atherosclerosis and endothelial dysfunction, the major causes of CSF, we hypothesized CHA2DS2-VASc score may be an important parameter associated with CSF. Therefore, we investigated the relationship between CHA2DS2-VASc score and CSF.

MATERIALS AND METHODS

We retrospectively collected the data of patients that applicant to cardiology department with SAP who were confirmed by CAG between January 2017 and July 2019. A total of 71 patients with angiographically proven CSF and age, sex matched 84 patients with angiographically proven normal coronary artery were enrolled in this study retrospectively. The control group consisted of consecutive subjects without heart failure, acute or chronic inflammation, and thyroid disorders.

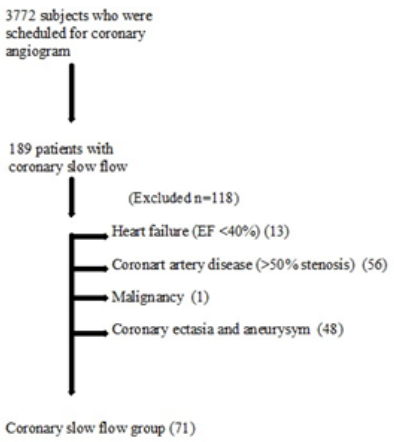

Figure 1. Flow chart

Two cardiologists who did not know the study protocol performed the selection of the participants. The patients with any epicardial coronary artery lesion with 50% or more stenosis were excluded from the CSF group regardless of whether obstructive lesion was in the CSF artery or not. The exclusion criteria were as follows: history of myocardial infarction, acute coronary events, any rhythm other than sinus, intracardiac conduction defect or branch block, left ventricular systolic dysfunction (LVEF≤40%), moderate or severe valve disease, chronic renal failure (estimated GFR<60 mL/min/1.73 m^2). (figure 1 flow chart). Patients who

showed slow flow in coronary angiography were divided into 2 separate subgroups according to CHA2DS2-VASc score. Patients with the CHA2DS2-VASc score > 1 were group A and patients with CHA2DS2-VASc score ≤1 were group B. By comparing these two subgroups, it was thought that the relationship between CHA2DS2-VASc score and timi frame count could be shown better.

The study protocol approved by the local ethics committee (Approval no: 04/07-02.03.2020) was explained to the patients and patients who accepted the protocol were included in the study upon reception of their written consent.

Coronary angiographic examination and diagnosis of CSF

Patients were selected from among individuals with SAP and documented coronary ischemia on exercise stress test or myocardial perfusion imaging. CAG was performed with the standard Judkins technique via the femoral route or radial route. Left coronary arteries were imaged by 6 or 7 F Judkins catheters with at least four projections (Spider position, right oblique, antero-posterior cranial, and left oblique) and right coronary arteries (RCA) with at least two exposures (left oblique and left cranial). Images were shot at a rate of at least 80 image frames and recorded at a rate of 25 frames per second.

Additional projections were taken in suspicious lesions and confirmed whether there was any lesion or not. Six to eight milliliters of opaque material were given by hand foreach exposure. A total of 50–100 cc non-ionic radiopaque substance was used for each patient. Nitrates were not administered in any of the study patients, as they cause significant enlargement of the artery with consequent increase in the volume to be filled with dye, thus increasing the thrombolysis in myocardial infarction frame count (TFC) by approximately 6 frames. We excluded patients with advanced heart failure (LVEF ≤40 %) and patients with CAD (≥50 % stenosis). We also excluded patients with pacemakers, as pacing may alter epicardial flow velocity All of the study patients had normal or near normal coronary aerteries defined as stenosis of 40% or less[4]. At least two cardiologists examined coronary anatomic examination records offline (ArtizZee, Siemens, Munich, Germany). The decision of the majority was accepted in the case of a conflict. Coronary blood flow velocity was determined by the quantitative number of framecount as described by Gibson et al.[4]. It is a reliable methodin all cardiology laboratories. We measured TFC as the difference of cine frames counts between proximal and distal coronary artery opacification. Bifurcation at the distal end of the left anterior descending coronary artery (LAD), and the point wherethe longest branch is distal to the circumflex artery (CX) (usually the branching of the optic margin branch or posterior descending branch separation), and posterolateral artery for the RCA are accepted as a distal point[3]. The normal TFC ranges were previously reported as 36.28± 2.6 for the LAD, 22.28± 4.1 forthe CX, and 20.48± 3.0 for the RCA. When there is an epicardial coronary artery with TFC higher than two standard deviations from the normal range, CSF is considered. Therefore, the cut-off values in diagnosis of CSF for LAD, CX, and RCA were determined as 41.48, 30.48, and 26.48, respectively. As LAD is 1.7 times longer than CX and RCA, the calculated TFC value for LAD is divided by 1.7, and the corrected TFC is obtained as 24.4. The mean TFC value is obtained by dividing the total TFC value by 3[3]. The interobserver variability of the TFC measurement was 1.9%.

Definitions

The CHA2DS2-VASc score was calculated by summing the scores assigned to each of the risk factors; modarate heart failure (1 point), hypertension (1 point), age ≥75 (2 points), diabetes mellitus (1 point), previous stroke, transient ischemic attack or thromboembolism (2 points), vascular disease (coronary artery stenosis <50%, peripheral artery disease or complex aortic plaques (1 point), 65-74 years (1 point) and female gender (1 point).

Based on the previous diagnosis of heart failure, he was diagnosed with congestive heart failure. Heart failure is defined according to the criteria proposed by the European Society of Cardiology working group on heart failure[13]. In at least two measurements, systolic blood pressure ≥ 140 mm-Hg and / or diastolic blood pressure ≥ 90 mm-Hg or antihypertensive drug use was defined as hypertension. Diabetes mellitus is defined if the patient is currently receiving antidiabetic drugs and / or insulin, or if his fasting blood sugar level is ≥126 mg/dL.

Stroke and transient ischemic attack were assessed by an anamnesis from the patient, and only events secondary to thromboembolism were included as a component of the CHA2DS2-VASc score. Peripheral artery disease was defined as ≥50%

stenosis in non-coronary arteries. Transthoracic echocardiography (Vivid 3; GE Medical System, Horten, Norway) was performed to patients in the first 24 hours of hospitalizations. LVEF was measured using modified Simpson's method.

Statistical analysis

All analyses were performed using SPSS for Windows version 18.0 (SPSS, Chicago, Illinois). Quantitative data are presented as means ± standart deviations (SD) for parametric variables or medians with interquartile ranges (lower and upper quartiles) for nonparametric variables. Kolmogorov-Smirnov test was used to assess the compatibility of our data with normal distribution. Then, student's t-test was used to compare normally distributed data between two groups and the Mann-Whitney U test was used for non-normally distributed data. The Pearson chi-square test was used in the investigation of categoric variables. Pearson and Spearman analyses were used for correlation analysis. Multiple linear regression analysis was performed for parameters affecting the presence of thrombus. Normally distributed data are expressed as means ± standard deviations and non-normally distributed data are expressed as percentage. P values less than 0.05 were tabulated as statistically significant. Receiver-operating characteristic (ROC) curves were estimated for CHA2DS2-VASc. ROC analysis was used to determine the cut-off values of CHA2DS2-VASc in predicting CSF. The sample power was measured using the Power and Sample Size Calculations program version 3.1.2, and it was 0.87.

RESULTS

The study population consisted of 155 patients (mean age, 54.7 [11.2] years and 30.9% female). Patients were classified into two groups: the CSF group (n=71) and (NCA) group (n=84). When the characteristics of the CSF and control groups were compared, age, body mass index (BMI), systolic blood pressure, diastolic blood pressure, gender were similar (all p values>0.05). Diabetes (20.2% vs. 38%, p=0.014), hyperlipidemia (27.3% vs. 46.4%, p=0.023), smoking rates (17.8% vs. 26.7%, p=0.003) were higher in the CSF group, LVEF (59.3±3 vs. 52.4±4), p=0.002) was higher in the NCA group.

Table-1. Demographic and clinical features of the patients.

Variable				
Age, years	53.07 ± 8.2	58.8 ± 7.3		0.382
Female gender, n (%)	23 (27.3%)	25	(35.2%)	0.031
Hypertension, n (%)	14 (16.6%)	21	(29.5%)	0.570
Smoking, n (%)	15 (17.8%)	19	(26.7%)	**0.003**
Diabetes mellitus, n (%)	17 (20.2%)	27 (38%)		**0.014**
Hyperlipidemia, n (%)	23 (27.3%)	33 (46.4%)		**0.023**
Body Mass Index, kg/m^2	24.6±3.6	26.2±4.1		0.160
LVEF, %, mean	59.3 ± 3	52.4 ± 4		**0.002**
History of moderate heart failure n (%)	1 (1.1%)	4 (5.6%)		**0.004**
History of stroke/TIA, n (%)	0		0	1
CHA2DS2-VASc score	1 [0-2]		2[1-3]	**<0.001**
Systolic blood pressure, mmHg	130 [108-145]	126 [105-138]		0.460
Diastolic blood pressure, mmHg	89 [72-96]	83[67-96]		0.230
Drug use, n (%)				
Acetyl salicylic acid	1 (1.1%)	3 (4.2%)		0.850
Beta blockers	5 (5.9%)	7 (9.8%)		0.230
Calcium channel blockers	6 (7.1%)	9	(12.6%)	0.170
ACEI/ARB	8 (9.5%)	12	(16.9%)	0.260
Statins	4 (4.7%)	7 (9.8%)		0.102

ACEI/ARB - angiotensin-converting-enzyme inhibitor/angiotensin-receptor blocker; LAD - left anterior descending artery; CX - circumflex artery; RCA - right coronary artery; HDL - high-density lipoprotein; LDL - low-density lipoprotein; TFC - thrombolysis in myocardial infarction frame count; LVEF – left ventriculer ejection fraction, NCA- normal coronary artery, CSF-coronary slow flow.

When the rates of cardiovascular drug use of both groups were compared, the rates of beta-blockers, acetylsalicylic acid, statin, calcium channel blockers, and angiotensin converting enzyme inhibitors/ angiotensin receptor blockers drug use were similar (all p values>0.05) (Table 1). Compared to both groups CHA2DS2-VASc score was higher in CSF group. (1[1], 2 [1], p<0.001) (Table-1) .

When biochemical variables of the CSF group and the control group were compared, the values of total cholesterol, triglycerides, high density-lipoprotein, low density-lipoprotein, creatinine, and haemoglobin were similar (p>0.05 for all values). Fastin glucose (109±18 vs. 123±24, p=0.002) was higher in CSF group. Compared to both groups TFC values, corrected LAD TFC (18±4 vs. 27± 5, p<0.001), CX TFC (14±3 vs. 23±4, p<0.001), RCA TFC (14±2 vs. 26±4, p<0.001), and the mean TFC (15±4 vs.26±6, p<0.001) was significantly higher in the CSF group than in the control group. (Table-2)

Table 2. Angiographic and laboratory features of the patients

Variable			
Glucose (mg/dL)	109±18	123±24	0.002
Serum creatinine, mg/dL	1.03± 0.38	1.1 ± 0.46	0.320
Hemoglobin, g/L	14.7 ± 1.6	13.2 ± 1,6	0.134
Total cholesterol, (mg/dL)	192±35	196±48	0.570
LDL-cholesterol, (mg/dL)	135 ± 28	141 ± 33	0.175
HDL-cholesterol, (mg/dL)	41±6	37±5	0.420
Trigylcerides (mg/dL)	162 [125-220]	158 [132-186]	0.147
Corrected LAD TFC	18±4	27±5	<0.001
Cx TFC	14±3	23±4	<0.001
RCA TFC	14±2	26±4	<0.001
Mean TFC	15±4	26±6	<0.001

LAD - left anterior descending artery; CX - circumflex artery; RCA - right coronary artery; HDL - high-density lipoprotein; LDL - low-density lipoprotein; TFC - thrombolysis in myocardial infarction frame count, NCA- normal coronary artery, CSF-coronary slow flow.

According to the CHA2DS2-VASc score, patients with CSF were divided into 2 subgroups. Patients with the CHA2DS2-VASc score > 1 were group A and patients with CHA2DS2-VASc score ≤1 were group B. Group A were the older, had a higher prevalence of female gender, and a lower EF compared with the group B. And also number of arteries with coronary slow flow was higher in group A (Table 3). Compared to both subgroups TFC values, corrected LAD TFC (29±5 vs. 23±5, p=0.021), CX TFC (24±4 vs. 19±3, p=0.017), RCA TFC (27±3 vs. 21±4, p=0.001), and the mean TFC (27±3 vs.21±5, p=0.003) was significantly higher in the group A than the group B.

Table 3. Demographic, clinical, and angiographic features of the subgroup coronary slow flow patients

Variable	**CHA2DS2-VASc score>1 (n=27)**	**CHA2DS2-VASc score≤1 (n=44)**	
Age, years	62±7.1	56±8.4	0.002
Female gender, n (%)	11 (40.7%)	14 (31.8%)	0.041
Hypertension, n (%)	9(33.3%)	12 (27.2%)	0.340
Smoking, n (%)	8 (29.6%)	11 (25.0%)	0.170
Diabetes mellitus, n (%)	11 (40.7%)	27 (36.3%)	0.164
Hyperlipidemia, n (%)	14 (51.8%)	19 (43.1%)	0.240
Body Mass Index, kg/m²	27.2±4.3	25.4±4.1	0.360
LVEF, %	47.5±6	55.3±3	0.001
Number of arteries w/ coronary slow flow	2 [1-3]	1 [1-2]	0.003
Corrected LAD TFC	29±5	23± 5	0.021
Cx TFC	24±4	19±3	0.017
RCA TFC	27±3	21±4	0.001
Mean TFC	27±3	21±5	0.003

LAD - left anterior descending artery; CX - circumflex artery; RCA - right coronary artery; TFC -thrombolysis in myocardial infarction frame count; LVEF – left ventricular ejection fraction.

In the regression analysis for the potential risk factors of CSF, variables with a significant P value in descriptive analysis were regressed separately on CSF. Results of univariate and multivariate analysis are shown in Table 3. Risk factors involved in CHA2DS2-VASc score were excluded from this analysis to avoid multicollinearity. Variables with a significant P value in univariate analysis were included into multivariate regression analysis. The multivariate analysis was repeated until all variables in the logistic regression were obtained to be significant. According to the results of the multivariate regression analysis, CHA2DS2-VASc score was an independent predictor (odds ratio [OR]:1.872, 95 % CI:0.849-1.981, p<0.00.1) (Table 4).

Table 4. Predictors of CSF

CHA2DS2-VAScs score	1.785(1.353-2.014)	<0.001	1.872(0.849-1.981)	<0.001
BMI	1.167(0.812-2.433)	0.710	1.232(0.940-2.008)	0.540
Smoking	0.737(0.621-0.953)	0.017	0.841(0.611-0.994)	0.19
HL	0.869(0.599-1.020)	0.210	0.782(0.592-0.997)	0.160

BMI- body mass index; HL- hyperlipidemia.

Nonparametric ROC analysis revealed the cutoff value of CHA2DS2-VASc score ≥ 1.5 as a predictor of CSF with a sensitivity of 69.2% and a specificity of 71.9%, area under curve: 0.809 with 95% CI (0.719-0.898) (F igure 2).

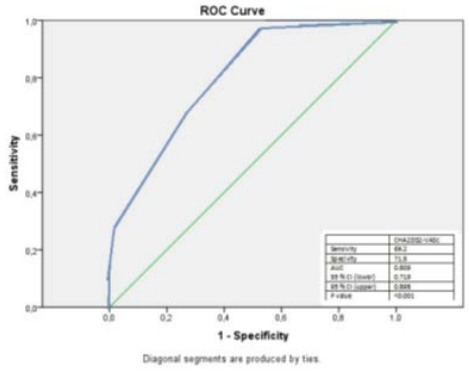

Figure 2. ROC curve analysis of the CHA2DS2-VASc score for predicting CSF

DISCUSSION

In this study, we showed that CHA2DS2-VASc score was significantly higher in patients with CSF. According to subgroup analysis, we found that there was a significant relationship between timi frame count increase and CHA2DS2-VASc score increase. To the best of our knowledge, this is the first study to determine the clinical utility of CHA2DS2-VASc score in predicting CSF. We also found CHA2DS2-VASc score ≥1.5 can be used as a cutoff value with a sensitivity of 69.2% and a specificity of 71.9%.

Coronary slow flow is defined as infirm coronary artery flow despite absence of significant coronary artery stenosis. Although it has been described more than forty years ago, the underlying mechanisms and prognostic consequences of CSF phenomenon are not fully understood. Miscellaneous mechanisms have been aforethought to have a role in the etiopathogenesis such as endothelial dysfunction, subclinical atherosclerosis, microvascular disease, vasomotor dysfunction, inflammation and oxidative stress. Intercalarily, It has shown that this is a systemic vascular abnormality rather than a local disorder[14,15]. These are the causes of atherosclerosis supporting the theory of the role of subclinical atherosclerosis in the pathogenesis of CSF. CSF is considered as a preliminary vascular disease that affects both resistive intramyocardial small and epicardial coronary arteries[16]. Many studies have investigated the long-term prognosis of CSF patients to be generally favorablein. Previously, CSF was reported to cause stable angina, but it has also been associated with both non ST elevation myocardial infarction and ST elevation myocardial infarction[17,18].

The CHA2DS2-VASc score is a set of risk factors for thromboembolism and stroke, as suggested by the current guidelines for use as a proven predictor of thromboembolic events among patients with AF[10,19]. Abnormal vascular function was recommended as a stroke mediator (20). Microvascular dysfunction also plays a role in CSF. Diabetes mellitus, one of the components of the CHA2DS2-VASc score, has been shown to be associated with impaired microvascular perfusion after percutaneous coronary intervention due to tendency to endothelium vasoconstriction and thrombosis[21,22]. Other components of CHA2DS2-VASc score; hypertension, diabetes mellitus, cardiomyopathy and female gender have also been shown to be predictors of coronary microvascular dysfunction23,24. Except for use in AF, the

CHA2DS2-VASc score was also identified as an appropriate and useful predictor of subsequent myocardial infarction, stroke, or death in patients with acute coronary syndrome and significant coronary stenosis prior to CAG[25,26].

Last of all, most of the risk factors for thromboembolism, endothelial and microvascular dysfunction coincide with those of CSF etiology. Atherosclerosis, vascular spasm, microvascular dysfunction, which are common risk factors for coronary slow flow and stroke, are associated with CHA2DS2-VASc score[27]. Given that the CHA2DS2-VASc score has a high predictive power of thromboembolic event and also includes common risk factors of CSF and thromboembolism, it can be considered as a priority in predicting risk in CSF. According to our data, we found that CHA2DS2-VASc score is independent indicators of CSF and can be used to predict CSF risk.

This current study had a number of limitations, including the lack of randomization, the retrospective observational design and the inclusion of patients from a single center study. Our results should be validated by a prospective, multicenter study. It is the small number of subjects. We detected NCA patients with visible angiograms that could cause bias in the randomization of the study population, and did not use intravascular ultrasound or optical coherence tomography. Other limitations of our study; we included heart failure in CH2ADS2-VASc score as modatere heart failure patients. Coronary flow may also slow down in these patients and since >50% coronary artery stenosis will affect coronary flow, we include patients with <50% stenosis as coronary artery disease in CH2ADS2-VASc score.

According to our analysis, CHA2DS2-VASc score to be an independent predictor of CSF. CHA2DS2-VASc score can be very useful as an easy-to-use tool. And also, our findings are evidence of thromboembolic and microvascular dysfunction in the etiopathogenesis of coronary slow flow. Therefore, we think that the treatment and follow-up of these patients should be the same as that of coronary artery patients.

Yazar Katkıları: Çalışma konsepti/Tasarımı: CK; Veri toplama: ÇZ, CK; Veri analizi ve yorumlama: CK; Yazı taslağı: ÇZ, CK; İçeriğin eleştirel incelenmesi: ÇZ, CK; Son onay ve sorumluluk: CK, ÇZ; Teknik ve malzeme desteği: CK; Süpervizyon: ÇZ; Fon sağlama (mevcut ise): yok.
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