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Original Article

The relationship between CHA_2DS_2-VASc score and isolated coronary artery ectasia

Hasan Ali Barman[1], Adem Atici[2], Gokhan Alici[3], Ramazan Asoglu[4], Gonul Aciksari[2], Sevil Tugrul[5], Irfan Sahin[5], Sait Mesut Dogan[1]

[1]Department of Cardiology, Institute of Cardiology, Istanbul University-Cerrahpaşa, Istanbul, Turkey; [2]Cardiology Department, Istanbul Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey; [3]Cardiology Department, Okmeydani Training and Research Hospital, Istanbul, Turkey; [4]Cardiology Department, Adiyaman Training ve Research Hospital, Adiyaman, Turkey; [5]Cardiology Department, Bagcilar Training ve Research Hospital, Istanbul, Turkey

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Abstract: Introduction: Coronary artery ectasia (CAE) is defined as localized or diffuse dilatation of the epicardial coronary arteries. We aimed to elucidate the relationship between the CHA_2DS_2-VASc score and CAE. Methods: The study population consisted of 122 patients with isolated CAE and 87 sex- and age-matched control subjects. The demographic, clinical, and laboratory profiles and CHA_2DS_2-VASc scores of patients with CAE and the control group were compared. The Markis classification was used to determine the extent of CAE. Coronary arteries in which ectasia was localized were identified. CHA_2DS_2-VASc scores were calculated for all patients. Parameters predicting the development of CAE were analyzed with multivariate logistic regression. Results: The majority of patients with CAE were male (76, 62%) and their mean age was 58.4 ± 8.3. The CHA_2DS_2-VASc score of the CAE group was significantly higher than that of the control group (2.41 ± 1.12 vs 1.52 ± 0.73, $P < 0.001$). Multivariate regression analysis showed that the CHA_2DS_2-VASc score (odds ratio [OR] = 1.607, $P = 0.004$), left ventricular ejection fraction (OR = 0.953, $P = 0.044$), uric acid (OR = 1.569, $P = 0.003$), white blood cell count (OR = 1.001, $P < 0.001$), highly sensitive C-reactive protein level (OR = 1.115, $P = 0.010$), and smoking (OR = 2.019, $P = 0.043$) were independent predictors of CAE. Conclusion: High CHA_2DS_2-VASc scores were associated with isolated CAE; therefore, the score might be a useful predictor of coronary thrombus development in patients with isolated CAE.

Keywords: CHA_2DS_2-VASc score, ectasia, coronary artery disease

Introduction

Coronary artery ectasia (CAE) is localized or diffuse dilation of the coronary artery lumen to at least 1.5 times the diameter of the adjacent healthy arterial segment [1]. Angiographic studies have found CAE rates of around 5%, while they are in the range of 0.22% to 1.4% in autopsy series [2-5]. Previous studies have shown that CAE patients also suffer from atherosclerosis (50-60%), congenital diseases (20-30%), and inflammatory or connective tissue diseases (10-20%) [1]. In addition, CAE is associated with coronary vasospasm, slow coronary flow, and thrombus formation in coronary arteries [6]. CAE causes ischemic heart disease, e.g., myocardial infarction, in the absence of obstructive coronary artery disease [7]. Although there are several risk scoring methods for heart diseases, no broadly accepted risk classification technique exists for measuring CAE. A simple, reliable, easily available, and practical scoring classification that is used to identify the cardioembolic risk and serves as an indicator of anticoagulant therapy in patients with non-valvular atrial fibrillation (AF) is the CHA_2DS_2-VASc (congestive heart failure/left ventricular dysfunction, hypertension, aged 75 years and over, diabetes mellitus, stroke/transient ischemic attack/systemic embolism, vascular disease, aged 65-74 years, sex category) stroke risk index [8]. The risk factors that are part of the CHA_2DS_2-VASc score are also related to coronary artery diseases. Recent studies have shown that the CHA_2DS_2-VASc score can independently predict ische-

mic stroke and cardiovascular events in coronary artery disease patients without AF [9, 10]. The relationship between the CHA_2DS_2-VASc score and CAE has not been studied to date. The objective of this study is to examine how the CHA_2DS_2-VASc score is related to CAE in patients undergoing elective coronary angiography.

Materials and methods

This prospective controlled study included 122 patients diagnosed with CAE using coronary angiography between October 2017 and January 2020. Patients without known coronary artery disease but with stable angina pectoris who underwent coronary angiography due to documented evidence of ischemia were included in the study. The control group of 87 subjects had normal coronary arteries. Patients with acute coronary syndrome, atrial fibrillation, severe liver or kidney failure, sepsis, malignancy, or moderate to severe valve diseases were excluded from the study. All study populations were evaluated by a cardiologist who used a questionnaire to obtain medical histories, which included demographic attributes, age, gender, results of a detailed physical assessment, smoking status, and diagnosis of diabetes mellitus (DM), hypertension (HT), and hyperlipidemia (HL). Complete transthoracic echocardiography was performed on all patients in accordance with the guidelines developed by the American Society of Echocardiography [11]. The modified Simpson approach was used to determine the left ventricular ejection fraction (LVEF). The presence of signs and symptoms of heart failure (HF) and a lower LVEF were indicative of congestive HF. An LVEF of ≤ 40% was indicative of moderate to severe systolic left ventricular dysfunction. The demographic, clinical, and laboratory profiles and CHA_2DS_2-VASc scores of patients with CAE and the control group were compared.

Systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, or the need to take antihypertensive medication was regarded as evidence of HT. A fasting blood sugar level of ≥ 126 mg/dL or the use of antidiabetic medicine was indicative of DM. A diagnosis of coronary artery disease, percutaneous coronary intervention, or peripheral artery disease (PAD) or previous myocardial infarction or bypass surgery was indicative of vascular disease. Diagnoses of PAD were made by confirmation of clinically symptomatic cases by objective Doppler and/or peripheral angiography. An ankle-brachial index (ABI) of less than 0.9 indicated PAD. Vascular disease referred to a history of myocardial infarction, aortic plaque, or PAD. A diagnosis of stroke was accepted when ischemia, hemorrhage, or an injured area in the brain was identified by clinical evaluations and imaging in patients presenting with neurological dysfunction and symptoms that lasted more than 24 hours. A transient ischemic attack was diagnosed when the neurological dysfunction lasted less than 24 hours and caused symptoms but did not result in death or disability. CHA_2DS_2-VASc scores were determined for all the study participants by awarding 1 point for HT, HF, age 65-74, DM, female sex, and vascular disease, and 2 points for age > 75 years and stroke (8). The maximum obtainable CHA_2DS_2-VASc score was nine.

Blood samples were obtained from all patients prior to coronary angiography. The tests were carried out 20 minutes after supine rest and fasting for 12 hours. The samples were placed in standard tubes containing of ethylenediaminetetraacetate acid (EDTA) for laboratory analysis. An automatic blood counter was used to immediately examine the blood samples. Levels of creatinine, uric acid, highly sensitive C-reactive protein (hs-CRP), and cholesterol were recorded. A hematology analyzer (LH 780, Beckman Coulter Inc., Miami, Florida) was used to examine hematological parameters, such as hematocrit, hemoglobin, and white blood cell (WBC) and platelet count. Written informed consent for the study was given by all participants. The Institutional Ethical Committee (IEC) approved the study in accordance with the Declaration of Helsinki. Ethical clearance was obtained from the IEC (Ref. No. 1466, date 11.05.2019) before conducting the research.

Coronary angiography

The presence of typical angina or positive or inconclusive findings of dobutamine stress echocardiography, treadmill exercise, or myocardial perfusion scintigraphy for myocardial ischemia in patients indicated coronary angiography. A coronary angiography device

(Integris BH 5000, Philips, the Netherlands) was used to perform angiography on all patients in accordance with guidelines [12]. The femoral approach employing 6-French (F) and 7-F Judkins catheters was used to perform selective coronary angiograms, which were then quantitatively analyzed (QCA, AET-met S.P.A., Italy). Two experienced interventional cardiologists, blinded to the patient's clinical data, reviewed all angiographic images. Luminal stenosis greater than 50% in any coronary vessel was regarded as demonstrating coronary artery disease [13]. CAE is a more than 1.5 times increase in the diameter of the coronary artery compared to that of adjacent healthy coronary vessels [1, 5]. A coronary artery segment without stenosis or ectasia was considered a healthy segment. If a normal segment could not be identified adjacent to the dilation, then the mean diameter of the comparable coronary section in the control group was considered the normal value. The number and distribution of coronary vessels affected by ectasia were determined using the Markis classification: type 1 = diffuse ectasia in two or three vessels; type 2 = diffuse ectasia in one vessel and focal ectasia in the rest of the vessels; type 3 = diffuse ectasia in one vessel; and type 4 = focal or segmental ectasia in one vessel [3].

Statistical analyses

The Statistical Package for the Social Sciences 19.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to perform all statistical tests. The normality of the data was tested using the Kolmogorov-Smirnov test. Continuous data are represented as mean ± SD and categorical data as percentages. The differences in categorical variables between groups were analyzed using a Chi-square test. Pearson's or Spearman's correlation analysis was used to examine relationships between parameters depending on the normality of the data. Unpaired samples were compared when necessary, using Student's *t*-test or Mann-Whitney *U* test. To identify the independent predictors, univariate logistic regression analyses were carried out. The variables that predicted CAE with a significant *P*-value were included in the multivariate analysis. The findings of univariate and multivariate regression analyses are given as odds ratio, with CI of 95%. Receiver operating characteristic (ROC) curve analysis was performed to determine the sensitivity and specificity of the CHA_2DS_2-VASc score and its cutoff value for predicting CAE. All statistical tests were two-tailed, and a *P*-value ≤ 0.05 was considered significant.

Results

The clinical and demographic characteristics of the study population are shown in **Table 1**. The mean age of the CAE group was higher than that of the control group (58.4 ± 8.3 years vs 56.6 ± 8.1 years; $P = 0.588$). The gender makeup was similar between the groups ($P = 0.12$). Seventy-six (62%) and 45 (51%) subjects were male in the CAE group and control group, respectively. HT, HF, DM, and smoking rates were significantly higher in the CAE group than in the control group, but HL and cerebrovascular events/transient ischemic attack (CVE/TIA) rates were similar between the groups. CAE patients had significantly higher CHA_2DS_2-VASc scores than the control subjects (2.41 ± 1.12 vs 1.52 ± 0.73; $P < 0.001$). LVEF, uric acid, WBC, and hs-CRP levels were significantly different between the groups. In contrast, creatinine, hemoglobin, hematocrit, and platelet count were similar. Markis classification scores were calculated for patients with CAE; the mean Markis score was 2.2. The number and distribution of coronary vessels affected by ectasia were determined using the Markis classification; 39 (32%) coronary vessels were type I, 36 (29%) were type II, 28 (23%) were type III, and 15 (19%) were type IV. According to the Markis classification, the left anterior descending artery (LAD) was 85 (69%), circumflex artery (CX) was 55 (45%), and right coronary artery (RCA) was 72 (59%) in CAE patients.

Variables related to the presence of CAE were analyzed with univariate and multivariate logistic regressions. The variables CHA_2DS_2-VASc score, LVEF, creatinine, uric acid, hemoglobin, platelet count, WBC, hs-CRP, HL, and smoking were analyzed with univariate logistic regression. Since CHA_2DS_2-VASc score, LVEF, uric acid, WBC, hs-CRP, and smoking were statistically significant in univariate analysis, they were evaluated using multivariate logistic regression analysis. CHA_2DS_2-VASc score, LVEF, uric acid, WBC, hs-CRP, and smoking were independently associated with the presence of CAE (an odds ratio of 1.607 [$P = 0.004$], 0.953 [$P = 0.044$], 1.569 [$P = 0.003$], 1.001 [$P <$

Table 1. The demographic and clinical data of the study population

	CAE (+) (n: 122)	CAE (-) (n: 87)	P
Age, years, mean ± SD	58.4 ± 8.3	56.6 ± 8.1	0.588
Male gender, n (%)	76 (62%)	45 (51%)	0.127
HF, n (%)	22 (18%)	7 (8%)	0.040
HT, n (%)	86 (70%)	45 (51%)	0.006
DM, n (%)	45 (36%)	20 (23%)	0.032
HLD, n (%)	40 (32%)	25 (28%)	0.533
CVE/TIA, n (%)	13 (10%)	3 (3%)	0.066
PAD, n (%)	-	-	-
Smoking, n (%)	73 (59%)	36 (41%)	0.008
CHA_2DS_2-VASc score	2.41 ± 1.12	1.52 ± 0.73	< 0.001
LV ejection fraction, (%)	51.4 ± 7.3	54.3 ± 7.9	0.007
Serum creatinine, mg/dl	0.8 ± 0.2	0.7 ± 0.1	0.102
Uric acid, mg/dl	5.2 ± 1.3	4.5 ± 1.1	< 0.001
Hemoglobin (g/dl)	13.5 ± 1.4	13.3 ± 1.8	0.458
Hematocrit (%)	40.9 ± 4.0	40.1 ± 4.7	0.168
Platelet counts, 10^3/μL	261.9 ± 75.2	249.0 ± 72.5	0.232
WBC, 10^3/μL	8.2 ± 2.3	6.4 ± 2.2	< 0.001
hs-CRP level, mg/l	21 (46-7)	8 (21-3)	< 0.001
Markis score	2.2 ± 1.06	-	< 0.001
CAE types, n (%)			
I, n (%)	39 (32%)		
II, n (%)	36 (29%)		
III, n (%)	28 (23%)		
IV, n (%)	15 (19%)		
CAE localization, n (%)			
LAD, n (%)	85 (69%)		
CX, n (%)	55 (45%)		
RCA, n (%)	72 (59%)		

Abbreviations: CAE, Coronary artery ectasia; HF, Heart failure; HT, Hypertension; DM, Diabetes mellitus; HLD, Hyperlipidemia; CVE, Cerebro vascular event; TIA, transient ischemic attack; PAD, Peripheral artery disease; LV, left ventricle; WBC, White blood cell; hs-CRP, high sensitivity C-reactive protein; LAD, Left anterior descending artery; CX, Cirkumflex artery; RCA, Right coronary artery.

0.001], 1.115 [P = 0.010], and 2.019 [P = 0.043], respectively; **Table 2**). In addition, CHA_2DS_2-VASc score parameters were analyzed using univariate and multivariate logistic regressions to predict the presence of CAE. HF, HT, age, and DM were statistically significant in univariate logistic regression analysis. HT and age were independent predictors of the presence of CAE (an odds ratio of 1.981 [P = 0.025] and 2.729 [P = 0.011], respectively; **Table 3**). In ROC curve analyses, a CHA_2DS_2-VASc score of 1.5 was determined as an effective cutoff point for CAE with a sensitivity of 73% and specificity of 51% (AUC = 0.71, 95% CI [0.64-0.78], P = 0.001; **Figure 1**). In addition, the Markis and CHA_2DS_2-VASc scores were significantly positively correlated (r = 0.603, P < 0.001; **Figure 2**).

Discussion

We investigated the relationship between the CHA_2DS_2-VASc score and CAE in patients who underwent elective coronary angiography. In this study, we report three major findings for patients with CAE. First, CAE patients had higher CHA_2DS_2-VASc scores compared to the control subjects. Second, CHA_2DS_2-VASc score was significantly and positively correlated with Markis score. Third, CHA_2DS_2-VASc score, LVEF, uric acid, WBC, hs-CRP, and smoking were independently associated with CAE.

Dilation of the coronary artery lumen to 1.5 times that of an adjacent normal segment is regarded as CAE [1]. Previous studies that used coronary angiography to diagnose coronary artery diseases have shown a CAE frequency of 0.3-4.9% [4, 5, 14]. CAE is most commonly experienced after the weakening of the coronary artery media layer [15]. Ectasia is most common in the RCA and least common in the left main coronary artery (LMCA) [16]. Registration data for 20,087 patients showed that CAE was most prevalent in the RCA [5]. Yip et al. also demonstrated that the RCA was the most ectatic vessel followed by the LAD and CX [17]. This study had a relatively small number of patients compared to previous studies, and CAE was observed mostly in the LAD and then in the RCA, CX, and LMCA in that order.

In Markis et al.'s study, type I ectasia was the most prevalent followed by type II, type III, and type IV in thirty patients with CAE [3]. Demopoulos et al. [18] reported that type III ectasia was the most common, whereas the other types occurred at a similar frequency. In

Table 2. Univariate and Multivariate logistic regression analysis to determine the independent predictors of coronary artery ectasia

Variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
CHA_2DS_2-VASc score	1.655	1.260-2.176	< 0.001	1.607	1.167-2.213	0.004
Ejection fraction	0.950	0.916-0.987	0.008	0.953	0.910-0.999	0.044
Creatinine	3.218	0.787-13.149	0.104			
Uric acid	1.506	1.186-1.911	0.001	1.569	1.172-2.101	0.003
Hemoglobin	1.067	0.899-1.266	0.457			
Platelet counts	1.002	0.998-1.006	0.232			
WBC	1.002	1.001-1.003	< 0.001	1.001	1.000-1.002	< 0.001
hs-CRP	1.158	1.048-1.281	0.004	1.155	1.035-1.290	0.010
HL	0.827	0.454-1.504	0.533			
Smoking	2.111	1.206-3.693	0.009	2.019	1.022-3.991	0.043

Abbreviations: CHA_2DS_2-VASc (Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥ 75 years, Diabetes Mellitus, Stroke/transient ischemic attack/systemic embolism, Vascular Disease, Age 65-74 years, Sex Category); WBC, White blood cell; hs-CRP, high sensitivity C-reactive protein; HL, Hyperlipidemia.

Table 3. Univariate and multivariate analysis of predictive power of individual components in CHA_2DS_2-VASc score for coronary artery ectasia

Variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
HF	2.514	1.022-6.184	0.045	1.865	0.715-4.869	0.203
HT	2.230	1.257-3.954	0.006	1.981	1.091-3.597	0.025
Age ≥ 75	-	-	-			
Age 65-74	2.457	1.160-5.201	0.019	2.729	1.255-5.930	0.011
DM	1.958	1.053-3.640	0.034	1.768	0.924-3.385	0.085
CVE, TIA	3.339	0.922-12.098	0.066	2.987	0.793-11.248	0.106
PAD	-	-	-			
Female gender	0.648	0.371-1.133	0.128			

Abbreviations: HF, Heart failure; HT, Hypertension; DM, Diabetes mellitus; CVE, Cerebro vascular event; TIA, transient ischemic attack; PAD, Peripheral artery disease.

agreement with Markis et al.'s study, we found that type I ectasia was most common and type IV the least common. Moreover, we demonstrated that the CHA_2DS_2-VASc score, which stratifies the thromboembolic risk, and the Markis classification score were significantly correlated in patients with CAE. These findings suggest that the CHA_2DS_2-VASc score might be a predictor of coronary thrombus formation in ectatic coronary segments in CAE patients. Markis et al. showed that HT was the more common cardiovascular disease in patients with CAE [3]. In their comparison of CAE patients with control subjects, Adiloglu et al. also found that HT was the more common cardiovascular disease in the former [19]. Several reports have proposed that HT may play an essential role in the pathogenesis of CAE and may accelerate the atherosclerotic destruction of the media layer of coronary arteries [20]. In this study, we demonstrated that HT is an independent predictor of ectasia in patients with CAE.

The pathophysiological mechanism of CAE is still unclear. An autopsy series reported advanced atherosclerotic changes in ectatic segments [21]. In addition to atherosclerotic lesion development, histological changes were observed in pathological assessments of the ectatic coronary segments. The atherosclerotic process generally impairs musculoelastic vessel elements, resulting in the thinning of the media layer of coronary arteries, which is typical of patients with CAE [2]. In addition, some studies have investigated other possible pathophysiological mechanisms of CAE [22, 23].

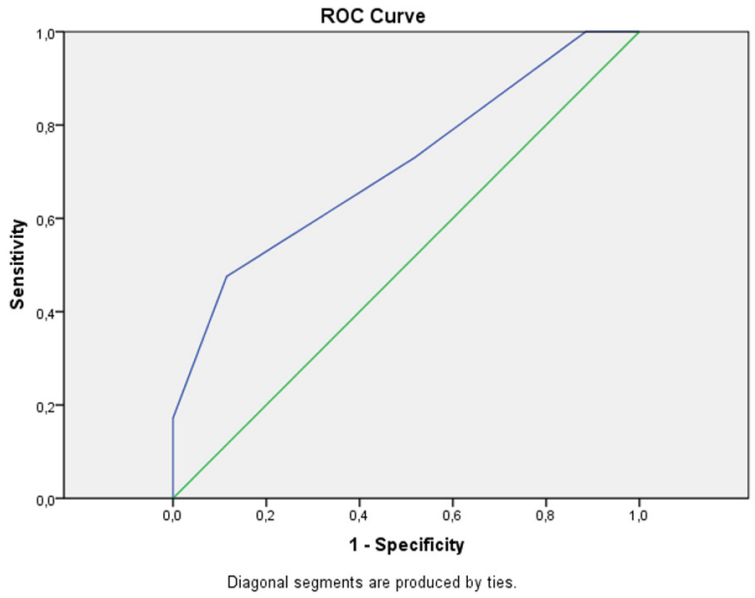

Figure 1. In ROC curve analyses, a CHA_2DS_2-VASc score of 1.5 was determined as an effective cut-off point in coronary artery ectasia with a sensitivity of 68% and a specificity of 73% and a specificity of 51% (AUC = 0.71, 95% CI (0.64-0.78), P = 0.001).

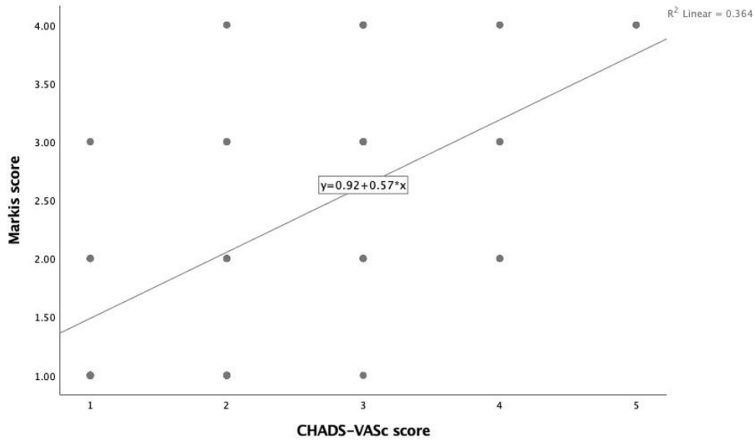

Figure 2. Correlation between CHA_2DS_2-VASc score and Markis score (r: 0.603, P < 0.001).

Yolcu et al. demonstrated that von Willebrand factor levels and plasminogen activator inhibitor-1 levels were significantly higher in CAE patients compared to control subjects [24]. Moreover, CAE is regarded as a vascular inflammatory disease [23]. The mechanism of ischemia is not known in CAE patients. Slow or turbulent coronary flow may result in coronary thrombosis and thromboembolism in ectatic segments [25]. Furthermore, turbulent coronary flow increased erythrocyte aggregations due to decreased laminar flow, and increased thrombogenicity and thromboembolism might be responsible for microvascular perfusion disorder in CAE [7, 26]. A previous study indicated that coronary flow rates are significantly decreased in coronary artery aneurysms compared to adjacent normal segments [27].

Due to risk factors for atherosclerosis that are similar in CAE patients [18], high CHA_2DS_2-VASc scores in CAE could be explained by these similarities. It is well known that smoking plays an essential role in the development of atherosclerosis, and it is one of the factors responsible for inflammatory changes in coronary vessels. Smoking impairs the vascular endothelium and increases platelet aggregation and monocyte entry into atherosclerotic lesions in coronary arteries [28, 29]. In this study, we showed that smoking was an independent predictor of the presence of CAE. The CHA_2DS_2-VASc score, which is simple, readily obtainable, and validated, is commonly used for predicting thromboembolism and indicating anticoagulant therapy for patients with nonvalvular AF [8]. Recent studies have demonstrated that the CHA_2DS_2-VASc score is an independent predictor of cardiovascular events, including ischemic stroke and death in patients without AF [30-32]. In this study, we showed that the CHA_2DS_2-VASc score was higher in patients with CAE compared to the control group. Moreover, in multivariate logistic regression analysis, we found that the CHA_2DS_2-VASc score was an independent predictor of the presence of CAE.

Limitations

The main limitation of our study is its small patient population. We diagnosed CAE visually,

and did not support the diagnosis by using an invasive diagnostic method, such as intravascular ultrasound, which provides information about the vessel wall. The other limitation of the study is the lack of laboratory tests to show thrombogenicity.

Conclusion

Our study showed that the CHA_2DS_2-VASc score was associated with ectasia in patients with isolated CAE. To our knowledge, this study is the first to evaluate this relationship. The CHA_2DS_2-VASc score may be a useful predictor of coronary thrombus development in isolated CAE patients. Larger prospective studies are necessary to assess the general use of CHA_2DS_2-VASc scores for diagnosing clinical conditions.

Disclosure of conflict of interest

None.

Address correspondence to: Hasan Ali Barman, Department of Cardiology, Institute of Cardiology, Istanbul University-Cerrahpaşa, Istanbul, Turkey. Tel: +90 506 326 19 25; Fax: +90 0212 221 78 00; E-mail: drhasanali@hotmail.com

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