The Novel CHA_2DS_2-VASC-FSH Score is Predictive of Severe Coronary Artery Disease on Coronary Angiography in Patients with Atrial Fibrillation and Unstable Symptoms

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ABSTRACT

Objective: AF may create confusion about the presence of severe or unstable coronary artery disease in cases with unstable symptoms. Novel scores and markers are needed to determine severe coronary artery disease in such patients. We aimed to test the newly developed CHA_2DS_2-VASc-FSH score, developed by adding family history for coronary artery disease, hyperlipidemia, and smoking to the original CHA_2DS_2-VASc score, in the prediction of severe CAD in patients with AF and unstable symptoms.

Materials and Methods: We retrospectively analyzed 72 patients presenting to Başkent Universtiy School of Medicine Hospital between April 2011 and January 2016. The CHA_2DS_2VASc-FSH score was assessed for the prediction of severe CAD.

Results: Seventy-two patients aged 65.7±11.2 years were enrolled. Thirty-five (48.6%) patients had severe CAD and 11 (15.3%) had unstable CAD. patients with severe coronary artery disease had a significantly greater CHA_2DS_2VASC-FSH score (5 (1-8) vs 3(0-7); $p<0.05$). The CHA_2DS_2VASC-FSH score independently predicted severe CAD, with a CHA_2DS_2VASc-FSH score of 3 or greater having a sensitivity of 77.1% and a specificity of 56.8% for severe CAD.

Conclusion: Among patients with AF and unstable symptoms, the CHA_2DS_2VASc-FSH score independently predicts severe CAD.

Keywords: Atrial fibrillation, coronary artery disease, CHA_2DS_2VASC-FSH score

Introduction

Atrial fibrillation (AF) is a common cause of emergency department admissions, particularly when associated with a rapid ventricular response [1]. AF may create myocardial ischemia or injury in the case of underlying severe coronary artery disease (CAD), but it may also mimic cardiac ischemia or infarction through elevated cardiac biomarkers and electrocardiogram (ECG) changes indicative of ischemia in the absence of underlying severe or unstable CAD [2]. Thus, there is a need for reliable predictors of severe or unstable CAD as the cause of signs and symptoms of patients with AF and unstable symptoms. It has been reported that the $CHADS_2$ and CHA_2DS_2-VASc scores, which were originally developed for the risk prediction of stroke and death [3-6], could predict severe CAD in various clinical settings [7-9]. Recently, the CHA_2DS_2-VASc-FSH score was formulated, which includes hyperlipidaemia, smoking, and the family history of CAD, in addition to the original CHA_2DS_2-VASc score, and substitutes the male gender for female gender. Hence, by incorporating the majority of risk factors for CAD, this newly developed score provides a comprehensive risk assessment for CAD [9]. The aim of this study was to determine the prevalence of severe CAD and the predictive ability of the newly developed CHA_2DS_2-VASc-FSH score for the prediction of severe CAD in comparison with conventional risk scores developed for AF, as well as other demographic, clinical, electrocardiographic, and biochemical parameters in patients with AF and unstable symptoms.

Materials and Methods

This study was approved by the Başkent University Institutional Review Board (Project No: KA17/104) and supported by the Başkent University Research Fund. We retrospectively analyzed the medical records of 72 patients older than 18 years who presented to the emergency department of Başkent University Faculty of Medicine Hospital between April 2011 and January 2016. All study subjects presented with symptomatic AF and unstable clinical symptoms sugges-

tive of cardiac ischemia, including chest pain or one or more of its equivalents, including resting dyspnea, palpitations, altered consciousness, syncope, diaphoresis, agitation, decompensated heart failure, or pulmonary edema, and all of them underwent invasive coronary angiography in the index hospitalization.

AF was classified into the categories of new-onset, paroxysmal, persistent, and permanent AF categories that were determined according to the 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society task force on practice guidelines, and the 2010 European Society of Cardiology Guidelines [10, 11]. Rapid ventricular response was defined as the resting heart rate greater than 100/min during AF at rest. Severe chronic renal disease referred to a severely (GFR ≤30 mL/min) or very severely (GFR ≤15 ml/min and/or receiving renal replacement therapy) reduced renal function (Stage 4 and 5 chronic kidney disease, respectively). Previous CAD was defined as invasively or non-invasively detected coronary luminal irregularities, plaques, or insignificant narrowings (≤50%) previously treated medically, and also significant (≥50%) lesions previously treated with either medical therapy, percutaneous coronary intervention, or coronary bypass surgery. The family history of CAD was defined as having a first degree relative diagnosed with CAD before the age of 65 for women and 55 for men. The history of smoking included past or current smoking. The history of heart failure included past or current signs and symptoms of heart failure with both low (<40%) and preserved ejection fraction (≥40%) and/or other objective evidence of cardiac dysfunction. Hypertension was defined as ongoing therapy for hypertension, systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg; diabetes mellitus (DM) was defined as a fasting blood glucose level >126 mg/dL or blood glucose ≥200 mg/dL, or using antidiabetic drugs; hyperlipidemia was defined as hypercholesterolemia (serum TC >5.72 mmol/L), high levels of LDL-c (>3.1 mmol/L), low levels of HDL-c (<0.9 mmol/L), hypertriglyceridemia (serum TG >1.70 mmol/L), or taking antihyperlipidemic medications. The history of ischemic cerebrovascular accident was defined as having a history of ischemic transient ischemic attack or ischemic cerebral stroke. Previous non-cerebral embolic events were defined as thromboembolic events in any organ other than the brain.

Cardiac biomarkers of injury, namely mass CK-MB and troponin I (cTnI), were measured both at admission and at 3 hours of follow-up. The cTnI testing was performed with an Architect STAT troponin I analyzer (Abbott Diagnostics, Illinois, USA) with a 99th percentile cut-off value of 0.01 μg/L. Numerical troponin I values and binary (present/absent) troponin I positivity were recorded at the admission and at follow-up. Troponin positivity referred to a troponin I measurement above the upper reference limit (URL). A delta troponin I change between the admission and follow-up troponin I values was recorded for every patient and defined by either as a 50% increase in the follow-up troponin I value compared to the admission value when the latter was below the URL, provided that either of the measurements was above the URL; or a 20% increase in the follow-up troponin I value when the admission value was above URL [12]. Renal function tests, electrolytes, and complete blood count parameters, including leucocyte count, neutrophil count, lymphocyte count, the red cell distribution width (RDW), hemoglobin level, platelet count, platelet-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio, were also measured.

Electrocardiographic changes suggestive of myocardial ischemia or injury were analyzed from 12-lead ECG recordings made at admission and 3-6 hours later, and they were defined as ≥1.0 mm horizontal or downsloping ST segment depression 0.08 seconds after the J point, symmetrical T inversion in at least two contagious precordial leads excluding V1 and V2, newly developed pathological Q waves defined as initial negative waves at least 0.04 sec in duration and 0.1 mv or >¼ of the proceeding R wave in size, or newly developed loss of the R wave progression across the precordial leads. Echocardiographic examinations were performed using a Vivid 7 Vingmed echocardiography device (Vingmed, GE, Horten, Norway). Echocardiographic left ventricular ejection fraction (LVEF) was determined by the modified Simpson's method, and systolic wall motion abnormality for each left ventricular segment was assessed by 2D echocardiography. Left ventricular hypertrophy was defined as interventricular septal and/or posterior left ventricular wall thicknesses exceeding 11 mm.

All patients in this study underwent invasive coronary angiography at consulting physician's discretion, on the basis of signs of symptoms suggesting acute cardiac ischemia or infarction. A significant coronary lesion was defined as luminal narrowing of ≥50% in any major epicardial vessel or one of its branches. In patients with a previous percutaneous coronary intervention, significant coronary lesions were defined as significant stent restenosis (≥50%) in previously stented vessels, or *de novo* significant luminal narrowing (≥50%) in previously untreated vessels. In patients who underwent a prior coronary bypass grafting operation, severe CAD was defined as significant *de novo* lesions in bypass grafts supplying one or more epicardial vessels, in non-bypassed coronary vessels, or in native vessels at sites distal to the insertion sites of bypass grafts. A non-significant coronary lesion was defined as luminal irregularities or plaques, or non-severe coronary lesions not exceeding 50%. The study population was classified into two groups depending on coronary angiography on invasive coronary angiography, and the two groups were compared with respect to the $CHADS_2$, CHA_2DS_2-VASc, and CHA_2DS_2-VASc-FSH scores, as well as demographic, clinical, electrocardiographic, echocardiographic, and laboratory results.

The $CHADS_2$ score was the sum of 1 point each for heart failure, hypertension (HT), age ≥75 years, and DM and 2 points for prior stroke or transient ischemic attack. The CHA_2DS_2-VASc score was calculated by assigning 1 point each for Congestive heart failure (CHF), HT, age 65-74 years, DM, vascular disease, and female gender and 2 points each for prior stroke or TIA and age ≥75 years. The newly formulated CHA_2DS_2-VASc-FSH score consists of CHF, HT, age ≥75 years (double score), DM, previous stroke/TIA (double score), vascular disease, age 65-74 years, gender (male), hyperlipidaemia, smoking, and a family history of CAD.

The exclusion criteria included asymptomatic AF cases, cardiovascular arrest or asystole, any wide complex tachyarrhythmia presumed or suspected to be of ventricular origin, presistent (>20 minutes) ST segment elevation; electrical cardioversion (pharmacological and spontaneous cardioversion were permissible) or chest compressions causing troponin I elevation; and recent history of myocardial infarction in the last 15 days. All study data were accessed via Başkent University Hospital's automation system.

Statistical Analysis

Continuous study data were presented as the mean±standard deviation or median (minimum-maximum) depending on the normality of their distribution assessed by the Kolmogorov-Smirnov test. Categoric variables were presented as the number and percentage. The difference between the groups with respect to continuous variables was tested with Student's t-test or the Mann-Whitney U test, with the former being used for normally distributed variables and the latter for non-normally distributed ones. The difference with regard to

Table 1. Clinical and pathologic characteristics of the patients

Characteristic	N (%)
Sex (male)	43 (59.7%)
Age (years)	65.7±11.2
Atrial fibrillation type	
New-onset	35 (48.6%)
Paroxysmal	13 (18.1%)
Persistent	4 (5.6%)
Permanent	20 (27.8%)
History of coronary artery disease	23 (31.9%)
Percutaneous coronary intervention (stenting)	6 (8.3%)
CABG	7 (9.7%)
CABG+stenting	2 (2.8%)
Medically treated	8 (11.1%)
Diabetes mellitus	25 (34.7%)
Hypertension	48 (66.7%)
Smoking	26 (36.1%)
Hyperlipidemia	31 (43.1%)
Severe renal disease	13 (18.1%)
Receiving dialysis	6 (8.3%)
Not on dialysis	7 (9.7%)
Heart failure	12 (16.7%)
Chronic obstructive pulmonary disease	9 (12.5%)
Thyroid disease	5 (6.9%)
History of cerebrovascular accident	7 (9.7%)
History of peripheral embolism	2 (2.8%)
Family history for coronary artery disease	10 (13.9%)
CHA2DS2–VASc score	3 (0-6)
CHA2DS2–VASc score ≥2	55 (76.4%)
CHA2DS2–VASc–HSF score	4 (0-8)
Medications used	
Beta blocker	17 (23.6%)
Non-dihydropyridine calcium channel blocker	7 (9.7%)
Digoxin	7 (9.7%)
Propafenone	2 (2.8%)
Amiodarone	1 (1.4%)
Warfarin Na	7 (9.7%)
NOAC	3 (4.2%)
Aspirin	21 (29.2%)
Clopidogrel	3 (4.2%)
ACE inhibitor	10 (13.9%)
ARB	11 (15.3%)
Dihidrooyridine calcium channel blocker	6 (8.4%)
Diuretic	19 (26.4%)
Insulin	6 (8.4%)
Oral antidiabetics	14 (19.4%)
Statins	6 (8.4%)
Thyroid medication	2 (2.8%)

Table 2. Findings on coronary angiography and coronary intervention results

Coronary angiography findings	
Severe coronary artery disease	35 (48.6%)
Single vessel disease	8 (22.9%)
Multivessel disease	27 (77.1%)
Non-severe coronary artery disease	37 (51.4%)
Normal coronary arteries	14 (37.8%)
Luminal irregularities	13 (35.1%)
Non-significant single vessel	3 (8.1%)
Non-significant multivessel	2 (5.4%)
Patent stent(s)	1 (2.7%)
Patent bypass graft(s)	4 (5.6%)
Unstable lesions	11 (15.3%)
Thrombosed lesion(s)	8 (22.9%)
Dissection	2 (5.4%)
Markedly slow flow	1 (2.7%)
Coronary intervention	24 (33.3%)
PCI	17 (70.8%)
CABG	7 (9.7%)
Stented vessel (or major branch[es] of)	
LMCA	1 (5.9%)
LAD	4 (23.5%)
Cx	6 (35.3%)
RCA	5 (29.4%)
2-vessel coronary disease	1 (5.9%)
Bypassed vessel (or major branch[es] of)	
LAD	6 (8.4%)
Cx	4 (5.6%)
RCA	4 (5.6%)

PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; LMCA: left main coronary artery; LAD: left anterior descending artery; Cx: circumflex artery; RCA: right coronary artery

categoric variables was tested using the chi-squared test. Two separate univariate analyses were then performed to determine the correlation between examined study parameters and severe CAD and unstable CAD on coronary angiography. A binary logistic regression analysis was performed to determine the significant independent predictors of severe CAD on coronary angiography.

Results

The overall study population consisted of 72 patients with a mean age of 65.7±11.2 years, of whom 43 were male and 29 were female. Thirty-five (48.6%) patients had new-onset AF; 13 (18.1%) patients had paroxysmal AF; 4 (5.6%) had persistent AF; and 20 (27.8%) had permanent AF. Twenty-six (36.1%) patients had a history of CAD, with 6 (8.3%) having a history of stent implantation, 7 (9.7%) having a history of coronary artery bypass grafting (CABG) operation, and 2 (2.8%) having a history of both stent implantation and CABG operation. Fifty-two (72.2%) patients presented with chest pain, of whom 46 (63.9%) had typical chest pain (Table 1).

A total of 30 (41.7%) patients had troponin I positivity at admission; 44 (61.1%) had follow-up troponin I positivity; 50 (69.4%) had overall troponin I positivity, and 38 (52.8%) had a clinically significant delta troponin I change.

Thirty-seven (51.4%) patients were not found to have severe coronary lesions. A total of 35 (48.6%) patients had severe single- or multivessel CAD on coronary angiography. Twenty-four (68.6%) patients with severe coronary lesions underwent coronary intervention. A total of 24 (33.3%) patients underwent coronary intervention. Among these, 7 (29.2%) underwent CABG; 17 (70.8%) underwent percutaneous coronary intervention and stenting (Table 2).

The comparison of the two groups with and without severe CAD revealed that the significant CAD group had significantly greater rates of hypertension, DM, CAD, CVA, severe renal disease, chest pain as the presenting symptom, and unstable lesions ($p<0.05$ for all comparisons); significantly greater CHA_2DS_2-VASc ($p<0.01$) and CHA_2DS_2-VASc-FSH scores ($p<0.05$), and significantly greater RDW and creatinine levels ($p<0.05$ for both). The two groups did not significantly differ with respect to cardiac biomarker levels, any troponin I positivity, ischemic ECG changes, echocardiographic wall motion abnormalities, or left ventricular hypertrophy (Table 3).

On univariate analysis, the rate of severe CAD was significantly correlated to the CHA_2DS_2-VASc score ($p<0.05$), The CHA_2DS_2-VASc-FSH score ($p<0.05$), hypertension ($p<0.05$), CAD ($p<0.05$), chronic severe renal disease ($p<005$), chest pain as the presenting symptom ($p<0.01$), creatinine ($p<0.01$), and RDW ($p<0.01$). A binary logistic regression analysis revealed that the CHA_2DS_2-VASC-FSH score (OR=1.80 [95% confidence interval (CI) 1.24-2.61]; $p<0.05$) and severe chronic renal disease (OR=7.96 [95% CI 1.46-43.51]; $p<0.05$) were the only significant predictors of severe CAD (Table 4). Among the three CAD prediction scores, the $CHADS_2$ score had an area under the curve (AUC) of 0.689 (0.567-0.811), the CHA_2DS_2-VASc score had an AUC of

Table 3. Comparison of the study groups with respect to demographic, biochemical, electrocardiographic, and echocardiographic variables

Parameter	Severe CAD (+) (n=35)	Severe CAD (-) (n=37)	p
Gender (male)	21 (60%)	22 (59.5%)	0.963
Age (years)	68.34 (11.74)	63.3 (10.3)	0.058
AF type			
New onset	21 (60%)	14 (37.8%)	0.112
Paroxysmal	4 (11.4%)	9 (24.3%)	
Peristent	0 (0%)	4 (10.8%)	
Permanent	10 (28.6%)	10 (27.0%)	
CAD	17 (48.6%)	7 (18.9%)	<0.05
DM	18 (51.4%)	7 (18.9%)	<0.05
HT	29 (82.9%)	19 (51.3%)	<0.05
Smoking	12 (34.3%)	14 (37.1%)	0.627
HL	19 (54.3%)	12 (32.4%)	0.063
CRD	12 (34.3%)	1 (2.7%)	<0.05
Heart failure	8 (22.9%)	4 (10.8%)	0.467
COPD	3 (8.6%)	7 (18.9%)	0.458
Thyroid disease	3 (8.6%)	2 (5.4%)	0.584
CVA	6 (17.1%)	1 (2.7%)	<0.05
History of peripheral embolism	1 (2.9%)	0 (0%)	0.782
CHA_2DS_2-VASc score	4 (0-6)	2 (0-5)	<0.01
CHA_2DS_2-VASc-HSF score	5 (1-8)	3 (0-7)	<0.05
Family history for CAD	4 (11.4%)	6 (16.2%)	0.563
Chest pain as the chief symptom	30 (85.7%)	22 (59.5%)	<0.05
Typical angina pectoris	26 (74.3%)	20 (54.1%)	0.075
Unstable lesions	11 (31.4%)	0 (0%)	<0.01
Admission troponin I (ng/mL)	0.91±3.08	1.57±4.64	0.491
Follow-up Troponin I (ng/mL)	0.42 (0-370.80)	0.06 (0-119.31)	0.428
Admission troponin I positivity	16 (45.7%)	14 (37.8%)	0.567
Follow-up troponin I positivity	25 (71.4%)	19 (51.4%)	0.166
Overall troponin I positivity	22 (62.9%)	20 (54.1%)	0.099
Delta troponin I change	23 (65.7%)	15 (40.5%)	0.078
Admission CK/MB (ng/mL)	3.62 ±3.65	3.33±4.17	0.759
Follow-up CK/MB (ng/mL)	7.59±4.55	5.33±11.49	0.150
Blood Urea Nitrogen (mg/dL)	20.66±7.82	21.14±12.94	0.855
Creatinine (mg/dL)	1.06 (0.61-5.31)	0.90 (0.66-4.45)	<0.05
Sodium (mEq/L)	137.34 ±4.11	137.78±3.19	0.631
Potassium (mEq/L)	3.86±1.31	4.05±0.85	0.487
Hemoglobin count (g/dL)	12.90±3.86	13.28±3.79	0.684
Leucocyte count (10^3/μL)	8.31±3.36	9.16±3.82	0.641
Neutrophil count (10^3/μL)	5.98 (2.06-38.21)	5.32 (3.25-19.50)	0.741
Platelet count (10^3/μL)	222.54±92.22	222.34±73.12	0.992
Lymphocyte count (10^3/μL)	2.10±1.16	2.33±2.62	0.232
NLR	3.59±2.76	3.83±3.14	0.098
PLR	130.43±73.86	131.18±72.59	0.967
RDW (%)	15.7 (12.0-21.7)	14.5 (11.5-22.7)	<0.05
Ischemic changes on ECG	14 (40.0%)	8 (21.6%)	0.095
Heart rate on ECG (bpm)	106.8±29.7	111.8±33.2	0.088
WMA	19 (54.3%)	13 (35.1%)	0.232
LVEF (%)	46.3±11.8)	49.8±11.9)	0.229
LVHT	25 (71.4%)	20 (54.1%)	0.192

CAD: coronary artery disease; DM: diabetes mellitus; HT: hypertension; HL: hyperlipidemia; CRD: chronic renal disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; RDW: red cell distribution width; ECG: electrocardiogram; LVEF: left ventricular ejection fraction; LVHT: left ventricular hypertrophy; WMA: wall motion abnormality on echocardiography

0.690 (0.568-0.813), and the CHA_2DS_2-VASc-FSH score an AUC of 0.703 (0.582-0.825). A CHA_2DS_2-VASc-FSH score of 3 or greater had a sensitivity of 77.1% and a specificity of 56.8% for predicting severe CAD (Figure 1).

The same correlation analyses were performed for patients with new-onset and paroxysmal AF (n=48). In univariate analysis, severe coronary lesions were correlated to the CHA_2DS_2-VASc score (p<0.05), CHA_2DS_2-VASc-FSH score (p<0.05), left ventricular hypertrophy (p<0.05), history of CAD (p<0.05), chronic severe renal disease (p<0.05), HT (p<0.05), creatinine (p<0.05), and chest pain as the chief presenting symptoms (p<0.05). On binary logistic regression analysis, the CHA_2DS_2-VASC-FSH score (OR=3.03 [95% CI 1.19-7.63]; p<0.05) remained the only significant predictor of severe CAD (Table 4). Among the three scores, the $CHADS_2$ score had an AUC of 0.670 (0.514-0.827); CHA_2DS_2-VASc score had an AUC of 0.671 (0.516-0.826), and the CHA_2DS_2-VASc-FSH score had an AUC of 0.679 (0.517-0.842). A CHA_2DS_2-VASc-FSH score of greater than 3 had a sensitivity of 80% and a specificity of 60.9% for predicting severe CAD (Figure 2).

Discussion

AF may complicate an acute coronary syndrome [13, 14], or it may also cause myocardial injury or infarction by creating a myocardial supply-demand mismatch (Type 2 myocardial ischemia), particularly when associated with rapid ventricular response, or by coronary embolism [15, 16]. Unfortunately, AF may also be associated with electrocardiographic ST-T changes and troponin positivity mimicking myocardial ischemia and injury in the absence of severe CAD [2]. It is often difficult to discern AF-induced pseudo-infarction/ischemia patterns from Type 2 myocardial ischemia resulting from underlying severe CAD, or a true acute coronary syndrome plus AF. Among patients with AF and unstable signs and symptoms, clinicians should determine the pretest probability of underlying severe or unstable CAD to make decisions about hospitalization and invasive coronary angiography.

So far, only a few studies have examined the prevalence and predictors of severe CAD in patients with AF and unstable symptoms and found prevalences ranging from 18.2% to 32.5% [17, 18]. Androulakis et al. [17] reported that there was no significant correlation between ischemic ECG changes and underlying occult CAD in patients with AF paroxysms. Alghamry et al. [18] found that dyspnea, ST depression, and a history of CAD predicted significant CAD

Table 4. Peredictors of severe CAD on coronary angiography in the overall AF and new-onset AF populations

		Univariate Analysis (p)	Binary Logistic Regression Analysis With Backward Wald Method (OR [95% CI])
Overall AF	Severe CAD	CHA_2DS_2-VASC-FSH (<0.05) CHA_2DS_2-VASC (<0.05) HT (<0.05) CAD (<0.05) CRD (<005) Chest pain (<0.01) Creatinine (0<0.01) RDW (<0.01)	CHA_2DS_2-VASC-FSH: 1.80 (1.24-2.61) CRD: 7.96 (1.46-43.51)
New-onset AF	Severe CAD	$CHA_2DS_2$2-VASC-FSH (<0.05) CHA_2DS_2-VASC (<0.05) LVHT (<0.05), CAD (<0.05) CRD (<0.05) HT (<0.05) Creatinine (<0.05) Chest pain (<0.05)	CHA_2DS_2-VASC-FSH: 3.03 (1.19-7.63)

AF: atrial fibrillation; CAD: coronary artery disease; HT: hypertension; CRD: chronic renal disease

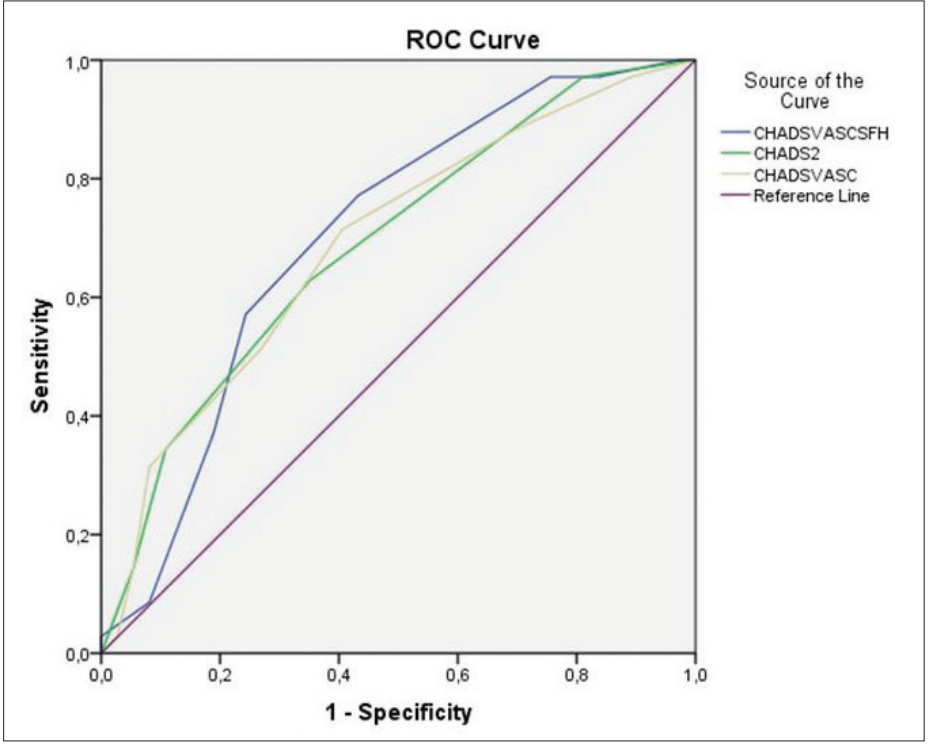

Figure 1. Receiver operating characteristics (ROC) curves of the thromboebolic risk scores in the prediction of severe coronary artery disease in the overall atrial fibrillation group.

in patients hospitalized for AF but concluded that troponin elevation was common among these patients and was not a reliable predictor for underlying severe coronary lesions. Our study revealed that among patients with AF and unstable symptoms the prevalence of severe CAD was 48.6%, and it revealed that neither cardiac biomarkers nor ischemic electrocardiographic changes were able to predict underlying severe CAD. On the other hand, CHA_2DS_2-VASc-FSH score and severe chronic renal disease emerged as significant independent predictors of severe CAD. Our results suggest that among patients presenting with AF and unstable symptoms, severe CAD can be independently predicted by the CHA_2DS_2-VASc-FSH score irrespective of the type of AF, so that a score of 3 or greater had a relatively fair sensitivity and a moderate specificity for severe CAD. Whereas the CHA_2DS_2-VASc score is originally designed to assess the risk of ischemic stroke and other thromboembolic events in AF [10], it gives an overall estimate of overall atherosclerotic burden on patients with AF since it incorporates many, albeit not all, risk factors for CAD. According to the Framingham study, AF and severe CAD share similar risk factors [19]. Given the multitude of common risk factors for both stroke and CAD, it has been suggested that CHA_2DS_2-VASc may provide aprognostic information in CHD without known AF [20]. In support of this view, the CHA_2DS_2-VASc score has been used for determining CAD severity in various populations other than in AF setting. Cetin et al. [7] reported that CHADS2, CHA_2DS_2-VASc, and especially CHA_2DS_2-VASc-HS scores could be considered predictive of the risk of severe CAD determined by the Gensini score among patients undergoing diagnostic coronary angiography who were in sinus rhythm. In a similar study, Modi et al. [9] reported that in 2976 consecutive patients, who were in sinus rhythm and underwent coronary angiography, CHADS2, CHA_2DS_2-VASc, and especially CHA_2DS_2-VASc-HS and CHA_2DS_2-VASc-HSF scores were predictive of the risk of severe CAD. Hioki et al. [20] reported that the CHA_2DS_2-VASc score was able to predict MACE at 1 year in patients undergoing percutaneous coronary intervention who were in sinus rhythm. Subsequently, a number of previous studies used the modifications of the original CHA_2DS_2-VASc for predicting the CAD severity in various settings. Cetin et al. [7] reported that the CHA_2DS_2-VASc-HS score, which added hyperlipidemia and smoking to the original score, was significantly better at predicting severe CAD, assessed by the Gensini score and the number of diseased vessels, than the original $CHADS_2$ and CHA_2DS_2-VASc scores in 407 consecutive patients undergoing coronary angiography. Uysal et al. [21] used the CHA_2DS_2-VASc-FSH score in patients with the ST elevation myocardial infarction. The authors reported that the score was significantly correlated to atherosclerosis severity assessed by the the SYNTAX score. Our study is noteworthy because, to the best of our knowledge, it is the first to use the CHA_2DS_2-VASc-FSH score in a population having AF and unstable signs and symptoms suggesting CAD. We used the newly developed CHA_2DS_2-VASc-FSH score instead of the CHA_2DS_2-VASc score because the former incorporates a greater number of risk factors for CAD and thus provides a greater clue about the underlying CAD than the traditional

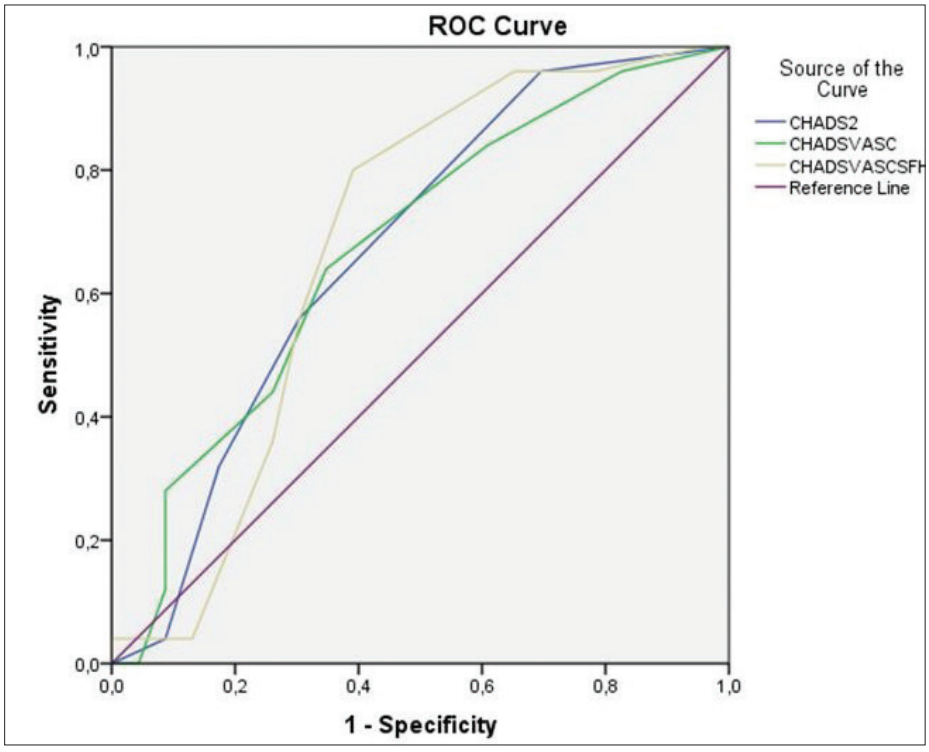

Figure 2. Receiver operating characteristics (ROC) curves of the thromboebolic risk scores in the ğrediction of severe coronary artery disease in the combined new-onset and paroxysmal atrial fibrillation groups.

CHA_2DS_2-VASc score. Supporting this idea, the CHA_2DS_2-VASc score was correlated to severe CAD in the univariate analysis, but it did not independently predict severe CAD in a multivariate analysis whereas the CHA_2DS_2-VASc-FSH score did. The CHA_2DS_2-VASc-FSH score was comparably predictive of significant CAD in early-stage AF types such as new-onset and paroxysmal AF, and the older AF types such as persistent and permanent AF. This suggests that it is the combination of risk factors and thus a greater CAD burden, but not the age of AF, that plays a role in the development of CAD, and the CHA_2DS_2-VASc-FSH score is equally predictive of severe underlying CAD in the overall AF population with unstable symptoms. It should also be noted that the CHA_2DS_2-VASc-FSH score helps provide the risk stratification not just in AF, but in all cases of ischemic heart disease, and it can be used in all of ischemic heart disease for prognostication. Therefore, its role as a prognostic sign should be further studied.

This study has some limitations. First, it was a retrospective analysis, and therefore it is limited by the inherent limitations of its design. Hence, it involved only patients with AF who underwent coronary angiography, and therefore the prevalence and the significant predictors of CAD remained unclear in the overall AF population, including the conservatively managed one. Furthermore, we lacked information about in-hospital or 30-day mortality and thus could not ascertain the prognostic value of the CHA_2DS_2-VASc-FSH score or delta troponin I change beyond coronary lesion characteristics. There is also a need for the validation of the CHA_2DS_2-VASc-FSH in other AF settings, such as in outpatients, postoperative period, and ST elevation myocardial infarction.

In conclusion, in patients with AF and unstable symptoms warranting further management, the newly defined CHA_2DS_2-VASc-FSH score can successfully predict severe CAD on coronary angiography. In clinical settings where clinical doubt exists whether symptoms are caused by severe CAD, or when severe CAD should be excluded for other purposes, a CHA_2DS_2-VASc-FSH score of at least 3 can be used to make a decision to proceed with invasive coronary angiography. In the future, the CHA_2DS_2-VASc-FSH score can be incorporated with other biochemical and echocardiographic predictors of atherosclerosis in patients with AF.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Başkent University Faculty of Medicine.

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

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