Cardiovascular Topics

The association between CHA_2DS_2-VASc score and aortic valve sclerosis

Funda Başyiğit, Havva Tuğba Gürsoy, Özlem Özcan Çelebi, Kevser Gülcihan Balcı, Özgül Uçar Elalmış, Kerem Özbek, Özge Çakmak Karaaslan, Mehmet İleri, Telat Keleş, Sinan Aydoğdu

Abstract

Background: Antithrombotic therapy in atrial fibrillation is generally managed with the CHA_2DS_2-VASc score. Aortic valve sclerosis (AVS) is a focal thickening of the aortic valve without a restriction of motion. AVS is related to several cardiovascular risk factors. Our study was performed to evaluate whether the presence of AVS was associated with the CHA_2DS_2-VASc score.

Methods: This cross-sectional, observational study comprised 411 patients with AVS grades 1–3 [AVS (+)] and 102 patients with AVS grade 0 [AVS (–)]. We compared CHA_2DS_2-VASc scores between the AVS (+) and AVS (–) groups.

Results: We determined that the AVS (+) group had a higher CHA_2DS_2-VASc score than the AVS (–) group [3 (0–8) vs 1 (0–4), $p < 0.001$)].

Conclusion: In our study, the CHA_2DS_2-VASc score was found to be higher in patients with AVS than in those without AVS. AVS may predict cardiovascular risk in the general population.

Keywords: aortic valve, atherosclerosis, coronary artery disease, inflammation

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The $CHADS_2$ and CHA_2DS_2-VASc scores are widely used to estimate stroke risk and guide antithrombotic therapy in patients with atrial fibrillation (AF).[1] Recent studies have shown that $CHADS_2$ and CHA_2DS_2-VASc scores, incorporating several cardiovascular (CV) risk factors, can also be helpful in different clinical situations besides AF. These scores have been demonstrated to have predictive values in terms of death in patients with stable coronary artery disease (CAD) and acute coronary syndromes.[2,3]

CHA_2DS_2-VASc, the updated version of $CHADS_2$, contains seven clinical variables, several of which are also CV risk factors, including congestive heart failure (CHF), hypertension (HT), age ≥ 75 years, diabetes mellitus (DM), stroke/transient ischaemic event, vascular disease, age 65 to 74 years and gender category (female). Kim *et al.* indicated in their study that higher CHA_2DS_2-VASc scores had worse CV outcomes in acute myocardial infarction patients.[3] Also recently, Shang *et al.* reported a correlation between the CHA_2DS_2-VASc score and the prevalence of carotid plaques.[4]

Aortic valve sclerosis (AVS) can be described by focal areas of thickening of the leaflets without a restriction of motion, with a peak velocity of less than 2.0 m/s.[5] It can easily be detected by transthoracic echocardiography (TTE), a safe, inexpensive and widely used imaging method.

In the past, it was believed that AVS was a degenerative disease associated with aging. However, the absence of AVS in approximately 50% of individuals above the age of 80 years suggested that different mechanisms play a role in its aetiology.[6] Today it is clear that AVS is not only simply a degenerative process but it also represents a complex process involving lipoprotein deposition, chronic inflammation and activation of the calcification cascade, similar to atherosclerosis.

Several studies have shown a relationship between atherosclerosis and AVS.[6-9] Although a direct connection has not been established, available data suggest that most components of the CHA_2DS_2-VASc score are also potential risk factors for atherosclerosis.[10] Therefore, a hypothesis that the CHA_2DS_2-VASc score may be associated with AVS seems plausible.

The correlation between the overall CHA_2DS_2-VASc score and AVS has not yet been studied. Based on this knowledge, we sought to design a cross-sectional study to search the relationship between the overall CHA_2DS_2-VASc score and AVS in patients without AF.

Methods

This was a single-centre, cross-sectional and observational study designed with patients aged > 18 and ≤ 75 years. We included 513 patients consecutively who had undergone TTE due to various clinical indications in the Ankara City Hospital cardiology clinic between March and December 2021.

AVS was defined as calcification and thickening of a three-leaflet aortic valve with an aortic velocity of < 2 m/s. Patients with

Department of Cardiology, Ankara City Hospital, Ankara, Turkey

Funda Başyiğit, MD, ftuna02@yahoo.com
Havva Tuğba Gürsoy, MD
Özlem Özcan Çelebi, MD
Kevser Gülcihan Balcı, MD
Özgül Uçar Elalmış, MD
Kerem Özbek, MD
Özge Çakmak Karaaslan, MD
Mehmet İleri, MD
Telat Keleş, MD
Sinan Aydoğdu, MD

AF, aortic velocity ≥ 2 m/s, severe valvular heart disease, bicuspid aortic valve, estimated glomerular filtration rate (eGFR) ≤ 15 ml/min, history of acute rheumatic fever, connective tissue disease and cancer were excluded. We analysed 411 patients with AVS grades 1–3 [AVS (+)] and 102 patients without AVS [AVS grade 0 AVS (–)].

The study protocol adhered to the ethical guidelines of the 2013 Declaration of Helsinki. This study was approved by the Ankara City Hospital Ethics Committee of the Ministry of Health Provincial Health Directorate (approval number E1-21-1638).

We collected detailed information on gender, age, medical history, co-morbidities, results of routine blood laboratory test parameters and electrocardiographic data from the electronic medical reports of our hospital. The eGFR values were calculated by the modification of diet in renal disease (MDRD) equations.

The CHA_2DS_2-VASc scores and diagnosis of all mentioned diseases of this score (CHF, HT, DM, stroke, vascular disease) were evaluated for each patient according to the current AF guideline of the European Society of Cardiology, published in 2020.[11] All patients underwent TTE, performed by two experienced cardiologists who were unaware of the clinical status of the patients, using the Philips Affinity50 echocardiography device.

The left ventricular posterior wall thickness (PWT), interventricular septal thickness (IVST), left ventricular end-diastolic diameter (LVEDD), left atrial diameter (LAD) and ascending aortic diameter were measured on the parasternal long-axis view. The left ventricular ejection fractions (LVEF) of the patients were calculated using Simpson's biplane method. We evaluated left ventricular diastolic dysfunction (LVDD) according to the update published by the American Society of Echocardiography and the European Association of CV Imaging.[12]

We assessed AVS from the parasternal long, parasternal short and apical five-chamber views. The presence of AVS was confirmed without using tissue harmonic imaging to avoid high gain settings.[13] We defined AVS as focal areas of increased echogenicity and thickening of the leaflets without a restriction of motion, and peak velocity of less than 2.0 m/s. We graded the severity of AVS on a scale of 0 to 3: 0 = normal (no involvement), 1 = mild (minor involvement of one leaflet), 2 = moderate (minor involvement of two leaflets or extensive involvement of one leaflet) and 3 = severe (extensive involvement of two leaflets or involvement of all three leaflets) (Fig. 1).[9] We defined AVS grade 0 as AVS (–) and AVS grades 1, 2 and 3 as AVS (+).

Statistical analysis

All data were analysed using the SPSS version 22.0 software (SPSS Inc, Chicago, IL). Continuous parametric data are summarised as means ± standard deviation (SD) and were compared by *t*-test analysis. We used the Pearson chi-squared

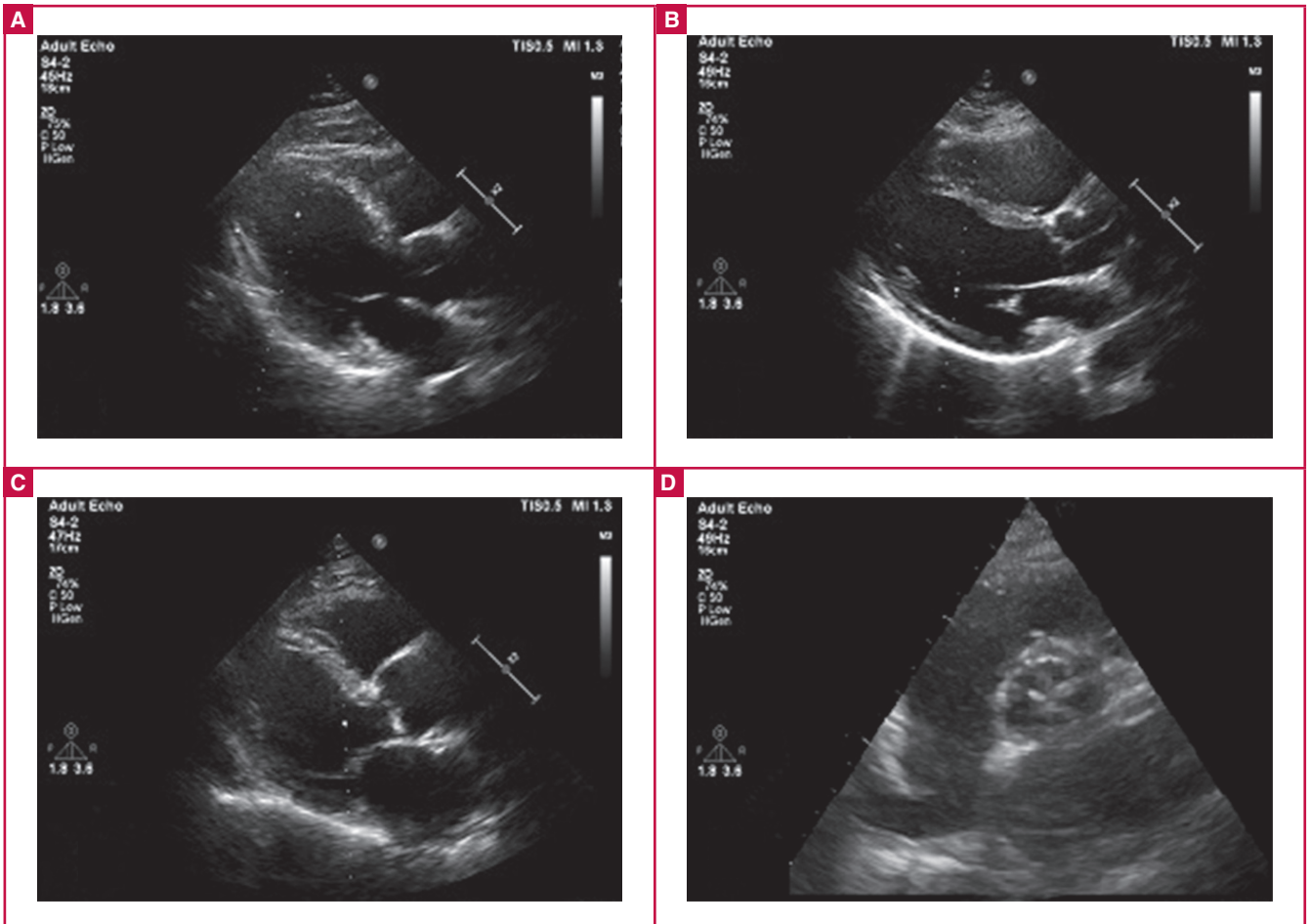

Fig. 1. Echocardiographic images of AVS grades showing (A) normal, (B) mild, (C) moderate, (D) severe grades.

test to compare categorical data and the Mann–Whitney *U*-test for non-parametric analysis. Univariate and multivariate logistic regression was also used to assess the association between AVS and CHA_2DS_2-VASc scores.

Fasting blood glucose (FBG), eGFR, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels; white blood cell (WBC) and neutrophil counts; PWT, IVST, LVEDD, LVDD, LAD, ascending aortic diameter, LVEF, insulin and statin therapies were adjusted in the multivariate logistic regression analysis. We used the area under the receiver operating characteristic (ROC) curve to determine the cut-off points of different CHA_2DS_2-VASc scores in AVS patients.

All tests were two-tailed and a p-value < 0.05 was considered statistically significant. Median CHA_2DS_2-VASc scores of AVS grades were compared with the Kruskal–Wallis *H*-test. The Spearman correlation test was used for the correlation of AVS grade and CHA_2DS_2-VASc score.

Results

We analysed 513 patients who underwent TTE because of different clinical indications [AVS grade 0, 102 (19.9%); AVS grade 1, 100 (19.5%); AVS grade 2, 134 (26.1%); AVS grade 3, 177 (34,5%)]. We divided patients into two groups according to detection of AVS (AVS grade 1–3) or not (AVS grade 0) (n = 411, 38.2% female, age 63.52 ± 7.24 years vs n = 102, 38.2% female; age 62.03 ± 5.26 years). The demographic and clinical data of participants are presented in Table 1. CHA_2DS_2-VASc scores of the study population and groups are shown in Fig. 2.

We determined that the AVS (+) group had a higher prevalence of CAD, stroke and peripheral artery disease (PAD) than the AVS (–) group (54.3 vs 13.7%; 11.9 vs 0%; 22.9 vs 2.9%, respectively, all p values < 0.001). We also determined that the patients in the AVS (+) group were older and had higher CHA_2DS_2-VASc scores (63.52 ± 7.24 vs 62.03 ± 5.26 years, p = 0.012; 3 (0–8) vs 1 (0–4), p < 0.001, respectively).

When we analysed TTE findings, we found that the AVS (+) group patients had lower LVEF and higher IVST, LAD and ascending aorta measurements when compared to the AVS (–) group (52.64 ± 10.76 vs 59.96 ± 4.55; 1.13 ± 0.14 vs 1.06 ± 0.11; 3.87 ± 0.45 vs 3.64 ± 0.3; 3.68 ± 1.73 vs 3.46 ± 0.29, respectively, all p-values < 0.001). LVDD was more common in the AVS (+) group than in the AVS (–) group (40.2 vs 70.3%, p < 0.001). We determined that oral antidiabetic (OAD) use, insulin and statin treatment rates were higher in the AVS (+) group than in the AVS (–) group (29.7 vs 11.7%, p = 0.001; 48.9 vs 19.6%, p < 0.001; 48.9 vs 19.6%, p < 0.001, respectively).

Table 1. Demographic and clinical data according to AVS

Demographics	*AVS (–)*, n = *102*	*AVS (+)*, n = *411*	p-*value*
Age, year	62.03 ± 5.26	63.52 ± 7.24	0.012
Gender, female, *n* (%)	39 (38.2)	157 (38.2)	0.995
Co-morbidities, *n* (%)			
DM	15 (14.7)	181 (44)	< 0.001
HT	54 (52.9)	382 (92.9)	< 0.001
CAD	14 (13.7)	223 (54.3)	< 0.001
CHF	1 (1)	97 (23.6)	< 0.001
Laboratory findings			
FBG, mg/dl (mmol/l)	101.69 ± 27.82 5.64 ± 1.54	119.65 ± 55.97 6.64 ± 3.11	0.024
Creatinine, mg/dl	0.82 ± 0.16	0.94 ± 0.31	0.001
TC, mg/l (mmol/l)	194.04 ± 44 5.03 ± 1.14	184.37 ± 45.84 4.78 ± 1.19	0.038
TG, mg/l (mmol/l)	162.86 ± 73.67 1.84 ± 0.83	174.18 ± 107.23 1.97 ± 1.21	0.646
HDL-C, mg/l (mmol/l)	47.28 ± 13 1.22 ± 0.34	43.23 ± 12.24 1.12 ± 0.32	0.012
LDL-C, mg/l (mmol/l)	114.1 ± 37.54 2.96 ± 0.97	107.3 ± 37.49 2.78 ± 0.97	0.043
WBC, × 10^3 cells/µl	6.98 ± 1.38	7.51 ± 1.79	0.035
Hb, g/dl	14.21 ± 1.47	13.71 ± 1.7	0.011
Plt, × 10^3 cells/µl	253.29 ± 59.07	267.44 ± 76.01	0.141
Echocardiographic findings			
LVEDD, cm	4.64 ± 0.36	4.80 ± 0.54	0.032
LVEF, %	59.96 ± 4.55	52.64 ± 10.76	< 0.001
PWT, cm	1.02 ± 0.1	1.08 ± 0.15	< 0.001
Aortic velocity, m/s	1.2 (1.0–1.9)	1.3 (1.0–1.9)	0.478
Ascending aorta diameter	3.46 ± 0.29	3.68 ± 1.73	< 0.001
LVDD, *n* (%)	41 (40.2)	289 (70.3)	< 0.001
CHA_2DS_2VASc score	1 (0–4)	3 (0–8)	< 0.001
CHA_2DS_2VASc ≥ 2	47 (46.0)	377 (91.7)	< 0.001
Drugs, *n* (%)			
ASA	34 (33.3)	251 (61.0)	< 0.001
Beta-blocker	25 (24.5)	269 (65.4)	< 0.001
ACE inhibitor	22 (21.5)	154 (37.4)	0.002
Statin	20 (19.6)	201 (48.9)	< 0.001
OAD	12 (11.7)	115 (27.9)	0.001
Insulin	1 (0.9)	53 (12.8)	< 0.001

ACE: angiotensin converting enzyme, ASA: acetylsalicylic acid, AVS: aortic valve sclerosis, CAD: coronary artery disease, CHF: congestive heart failure, DM: diabetes mellitus, FBG: fasting blood glucose, Hb: haemoglobin, HDL-C: high-density lipoprotein cholesterol, HT: hypertension, LDL-C: low-density lipoprotein cholesterol, LVDD: left ventricular diastolic dysfunction, LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, OAD: oral antidiabetic, Plt: platelets, PWT: posterior wall thickness, TC: total cholesterol, TG: triglyceride, WBC: white blood cells.

A cut-off value of ≥ 2 for the CHA_2DS_2-VASc score was estimated to evaluate AVS, which had a sensitivity of 81.2% and specificity of 65.7%, area under the curve (AUC) of 0.833 with 95% CI (0.792–0.874) (Fig. 3). Patients with CHA_2DS_2-VASc

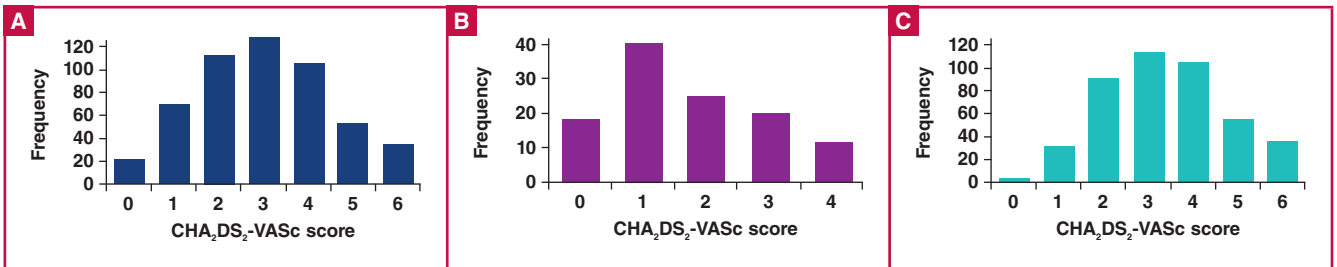

Fig. 2. CHA_2DS_2-VASc scores (A) in the study population, (B) in the AVS (–) group and (C) in the AVS (+) group.

Table 2. Odds ratio and 95% CI between the CHA_2DS_2VASc score and prevalence of AVS

	Univariate		*Multivariate*	
Variables	*Odds ratio (95% CI)*	p-*value*	*Odds ratio (95% CI)*	p-*value*
CHA_2DS_2-VASc ≥ 2	12.976 (7.684– 21.916)	< 0.001	7.366 (3.452–15.722)	< 0.001
FBG	1.011 (1.004–1.018)	0.004	0.995 (0.987–1.003)	0.251
TC	0.995 (0.99–1)	0.042	0.996 (0.977–1.017)	0.729
TG	1.001 (0.999–1.004)	0.294		
HDL-C	0.976 (0.959–0.994)	0.008	1.012 (0.983–1.042)	0.414
LDL-C	0.994 (0.988–1)	0.039	1.003 (0.981–1.026)	0.763
LVEF	0.846 (0.8–0.893)	0.000	0.873 (0.816–0.934)	< 0.001
LVEDD	2.196 (1.265–3.814)	0.005	0.493 (0.186–1.309)	0.156
IVST	74.842 (14.038–399.011)	< 0.001	3.515 (0.121–102.031)	0.465
PWT	23.448 (4.783–114.954)	< 0.001	7.209 (0.419–124.018)	0.174
LVDD	3.524 (2.250–5.521)	< 0.001	0.943 (0.491–1.814)	0.861
LAD	5.488 (2.807–10.73)	< 0.001	1.162 (0.408–3.308)	0.779
Asc. aorta dia.	3.798 (1.904–7.575)	< 0.001	4.697 (1.758–12.549)	0.002
eGFR	0.97 (0.955–0.985)	< 0.001	1.006 (0.985–1.027)	0.563
WBC	1.199 (1.044–1.378)	0.010	0.784 (0.525–1.171)	0.234
Neutrophils	1.432 (1.179–1.738)	< 0.001	1.682 (0.993–2.85)	0.053
Insulin therapy	14.846 (2.028–108.688)	0.008	12.926 (1.246–134.103)	0.032
Statin therapy	3.952 (2.334–6.691)	< 0.001	1.814 (0.918–3.582)	0.087

Asc. aorta dia: ascending aorta diameter, FBG: fasting blood glucose, eGFR: estimated glomerular filtration rate, HDL-C: high-density lipoprotein cholesterol, LAD: left atrial diameter, LDL-C: low-density lipoprotein cholesterol, LVDD: left ventricular diastolic dysfunction, LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, IVST: interventricular septal thickness, OR: odds ratio, PWT: posterior wall thickness, TC: total cholesterol, TG: triglyceride, WBC: white blood cells.

score ≥ 2 were 7.366-fold (95% CI: 3.452–15.722) more likely to develop AVS compared with those who had a CHA_2DS_2-VASc score < 2 (Table 2).

In the univariate logistic regression analysis, CHA_2DS_2-VASc score ≥ 2, FBG, HDL-C, LVEF, LVEDD, PWT, IVST, LAD, ascending aortic diameter, eGFR, WBC, neutrophil, insulin and statin therapies were found to be predictors of AVS. Moreover, we determined that CHA_2DS_2-VASc score ≥ 2, LVEF and ascending aortic diameter were independent predictors of AVS (Table 2).

Median CHA_2DS_2-VASc scores among the AVS grades are shown in Fig. 4. We determined that median CHA_2DS_2-VASc scores showed a significant difference according to AVS grade [grade 0, n = 102, 1 (0–4); grade 1, n = 100, 3 (0–7); grade 2, n = 134, 3 (0–7); grade 3, n = 177, 4 (1–8), H (3) = 160,935, p < 0.001), respectively]. Median CHA_2DS_2-VASc scores of grades 0 and 1 and grades 2 and 3 were significantly different. On the other hand, median CHA_2DS_2-VASc scores of grades 1 and 2 were similar [1 (0–4) vs 3 (0–7), p = 0.001; 3 (0–7) vs 4 (1–8), p = 0.001, 3 (0–7) vs 3 (0–7), p = 0.26, respectively]. Also, to investigate whether AVS grade correlated with CHA_2DS_2-VASc score, Spearman correlation analysis was performed. A positive correlation was determined between AVS grade and CHA_2DS_2-VASc score (r = 0.548, p < 0.001).

Discussion

The results of our study indicate three main findings: first, CHA_2DS_2-VASc ≥ 2 score was independently associated with AVS; second, the cut-off point of the CHA_2DS_2-VASc score to predict AVS was ≥ 2; finally, there was a positive correlation between the grade of AVS and the CHA_2DS_2-VASc score.

The CHA_2DS_2-VASc score was initially designed for predicting embolic events and adjusting antithrombotic therapy in AF patients. This score drew attention because it included many CV risk factors together, and several studies encompassed it in different clinical settings. The CHA_2DS_2-VASc score was found to have predictive value both in acute and chronic coronary syndromes.[2,3]

Recently, Shang *et al.* detected a correlation between the CHA_2DS_2-VASc score and carotid plaques, known as a marker of subclinical atherosclerosis. Similarly, we determined an association between CHA_2DS_2-VASc score and AVS, a marker of subclinical atherosclerosis. These results suggest that CHA_2DS_2-VASc score may be associated not only with clinical

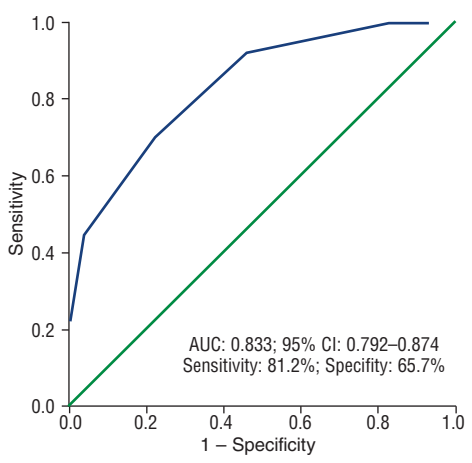

Fig. 3. ROC curves for CHA_2DS_2VASc score in order to evaluate AVS. The area under the ROC curve was utilised to figure out cut-off points of different CHA_2DS_2-VASc scores in AVS patients.

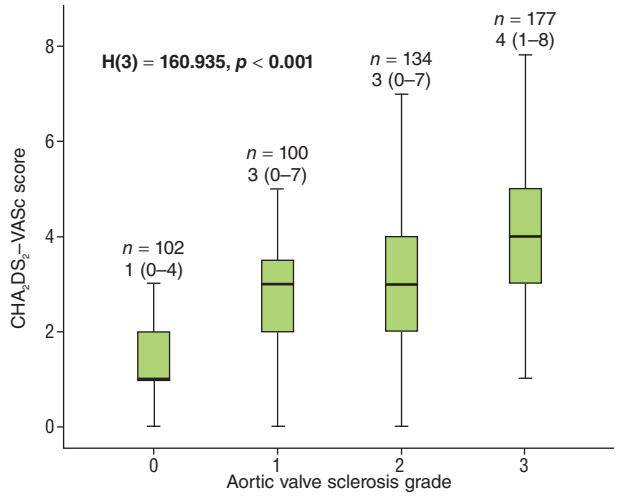

Fig. 4. Median CHA_2DS_2-VASc scores according to AVS grades. Median CHA_2DS_2-VASc scores of AVS grades were compared with the Kruskal–Wallis H-test.

atherosclerosis but also with subclinical atherosclerosis.

Shang *et al*. reported that CHA_2DS_2-VASc scores ≥ 2 in males and ≥ 3 in females were associated with carotid plaques. They also showed that male patients with a CHA_2DS_2-VASc score ≥ 2 had a 2.3-fold increased risk of developing carotid plaques.[4] On the other hand, in our study, patients with CHA_2DS_2-VASc score ≥ 2 had a 7.4-fold increased risk of developing AVS than those with a CHA_2DS_2-VASc score < 2.

Previous studies have shown the relationship between AVS and CV risk factors and morbidity and mortality.[14,15] On the other hand, Rosa *et al.* reported that AVS was not associated with a higher risk of death and cardiac death.[16] However, a meta-analysis by Pradelli *et al*. showed that increased absolute event rate in subjects with AVS reduced when the other known CV risks were taken into account. Therefore we believe that the negative association between AVS and cardiac death might be due to the higher baseline CV risks of the patient subgroups included in the study by Rosa *et al*.[17]

On the contrary, there are studies showing the association of AVS and CV mortality and morbidity in high-risk populations.[18,19] Our results showing the association between AVS and CHA_2DS_2-VASc score may contribute more information to this argument. Nevertheless, the results of our study do not allow us to support the correlation between CV prognosis and CHA_2DS_2-VASc score in AVS. Further studies should be designed to ascertain this issue.

Our study determined that LVEF was lower in patients with AVS than in those without AVS. In our multivariate analysis, LVEF was also found to be an independent predictor of AVS. This may be explained by increased atherosclerotic burden leading to a decrease in LVEF in patients with AVS. Also, clinical studies show that low wall shear stress plays a significant role in the initiation of atherosclerosis within the coronary arterial wall and the progression of calcium deposition on the leaflets. In the same way, the non-coronary cusp was found to be affected initially, probably due to the low shear stress on the endothelium in diastole, given the absence of diastolic coronary flow in this cusp.[6] Likewise, as LVEF decreased, shear stress through the aortic valve might decrease. Reduced shear stress might lead to repetitive injury and inflammation, progressive thickening and calcification of the aortic valve leaflets.

LVEDD, PWT, IVST, LAD and ascending aorta measurements by TTE were statistically higher in patients with AVS compared to patients without AVS in our study. This can be explained by the higher prevalence of HT in AVS, as was also observed in our study. We also detected LVDD more often in the AVS (+) than in the AVS (–) group. Both AVS and LVDD have been reported to be related to many CV risk factors, especially HT and DM and this may explain the relationship we found between them.[20,21] DM, FBG level, as well as OAD and insulin therapies were statistically higher in the AVS (+) group in our study.

Although hyperlipidaemia is a risk factor for AVS, TC and LDL-C levels were lower in the AVS (+) group. It might be because of the high prevalence of patients with hyperlipidaemia in the AVS (+) group using statins.

Inflammation plays a critical role in both the pathophysiology of AVS and atherosclerosis.[9] We also determined that WBC and neutrophil counts were higher in patients with AVS than in those without AVS. Additionally, we detected a correlation between AVS grade and CHA_2DS_2-VASc score. Our study is the first to report the relationship between AVS and CHA2DS2-VASc score and show a progressive rise in CHA_2DS_2-VASc score along with the grade of AVS. It seems logical to control risk factors for AVS as one would for CAD.

There are several limitations in our study. First, it was a single-centre, cross-sectional and observational study having the limits inherent in its design. Second, data of the study population were obtained from the electronic medical report of our hospital, which had a selective bias. Third, unfortunately, we could not find a universally accepted AVS definition in the literature. A prospective cohort study to more accurately determine the prognostic value of the CHA_2DS_2-VASc score is necessary.

Conclusion

CHA_2DS_2-VASc score was higher in patients with AVS compared to those without AVS. Furthermore, the CHA_2DS_2-VASc score increased as the AVS grade increased. The pathophysiology of AVS is thought to have an inflammatory component besides a degenerative process, which is related to CV diseases. TTE, commonly used clinically, can easily detect AVS. A diagnosis of AVS might change the treatment goals of patients to decrease CV risk in the population.

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