

## Prognostic predictive value of CHA<sub>2</sub>DS<sub>2</sub>-VA score in patients with permanent atrial fibrillation

Serdar Söner<sup>1</sup>, Oktay Şenöz<sup>2</sup>

<sup>1</sup>Department of Cardiology, Health Science University, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye

<sup>2</sup>Department of Cardiology, Bakırçay University, Çiğli Training and Research Hospital, İzmir, Türkiye

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### ABSTRACT

**Objectives:** This study aims to investigate the prognostic value of the CHA<sub>2</sub>DS<sub>2</sub>-VA score in patients with permanent atrial fibrillation (AF).

**Patients and methods:** Between January 2023 and June 2023, a total of 917 patients with permanent AF (446 males, 471 females; mean age: 70.2±9.7 years; range, 27 to 89 years) were retrospectively analyzed. The patients were divided into two groups based on their CHA<sub>2</sub>DS<sub>2</sub>-VA scores: high-risk (score ≥2, n=743) and low-risk (score <2, n=174). Data on one-year all-cause mortality were collected through follow-ups and interviews.

**Results:** In the univariate analysis, CHA<sub>2</sub>DS<sub>2</sub>-VA score, age, sex, systolic blood pressure (SBP), left ventricular ejection fraction (LVEF), chronic obstructive pulmonary disease (COPD), chronic kidney disease, hemoglobin, neutrophil, and lymphocyte counts were found to be significant predictors of mortality. Multivariate analysis revealed that only age, sex, SBP, COPD, LVEF, and hemoglobin were independent predictors. There was a significant relationship between CHA<sub>2</sub>DS<sub>2</sub>-VA score and one-year all-cause mortality (p=0.002).

**Conclusion:** Our study results showed that the CHA<sub>2</sub>DS<sub>2</sub>-VA score was associated with one-year all-cause mortality in AF patients, but it was not an independent predictor when evaluated with all parameters affecting mortality. In the management of AF patients, the CHA<sub>2</sub>DS<sub>2</sub>-VA score may be useful not only in determining oral anticoagulation strategy, but also in the approach of clinicians to AF patients, considering that it may be a predictor of mortality.

**Keywords:** All-cause mortality CHA<sub>2</sub>DS<sub>2</sub>-VA score, permanent atrial fibrillation.

Atrial fibrillation (AF) is the most prevalent persistent arrhythmia, which significantly and adversely affects the quality of life and increases mortality and morbidity rates.<sup>[1]</sup> Preventing thromboembolism is the main goal to reduce the overall mortality rate associated with AF. Indeed, compared to a placebo or control, oral anticoagulation with Vitamin K antagonists (VKAs) dramatically lowers stroke and systemic embolism by 64%, while also significantly lowering all-cause mortality by 26%.<sup>[2]</sup> Numerous extensive randomized studies have shown that non-Vitamin K oral anticoagulants (NOACs) are safe and effective.<sup>[3-6]</sup> Over the last decade, NOAC use has become widespread due to the impact of these studies and as NOAC use does not require international normalized ratio (INR) monitoring.

One commonly used metric to estimate the risk of thromboembolic events in individuals with AF

was the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 and sex category [female]). Physicians widely used the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, since it is straightforward: it does not require an online calculation, each point is assigned to a binary risk factor, and it does not require laboratory or radiographic testing. Numerous conventional coronary artery disease (CAD) risk

**Corresponding author:** Serdar Söner, MD. Sağlık Bilimleri Üniversitesi, Gazi Yaşargil Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, 21070 Kayapınar, Diyarbakır, Türkiye  
E-mail: drserdar\_89@hotmail.com

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factors are also included in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Therefore, independent of the occurrence of AF, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is a good predictor of both in-hospital and long-term unfavorable cardiovascular events. All-cause mortality, non-fatal myocardial infarction, acute stent thrombosis, no-reflow phenomenon, non-fatal stroke, pulmonary embolism, and other adverse cardiovascular events have been linked to high CHA<sub>2</sub>DS<sub>2</sub>-VASc scores.<sup>[7-13]</sup>

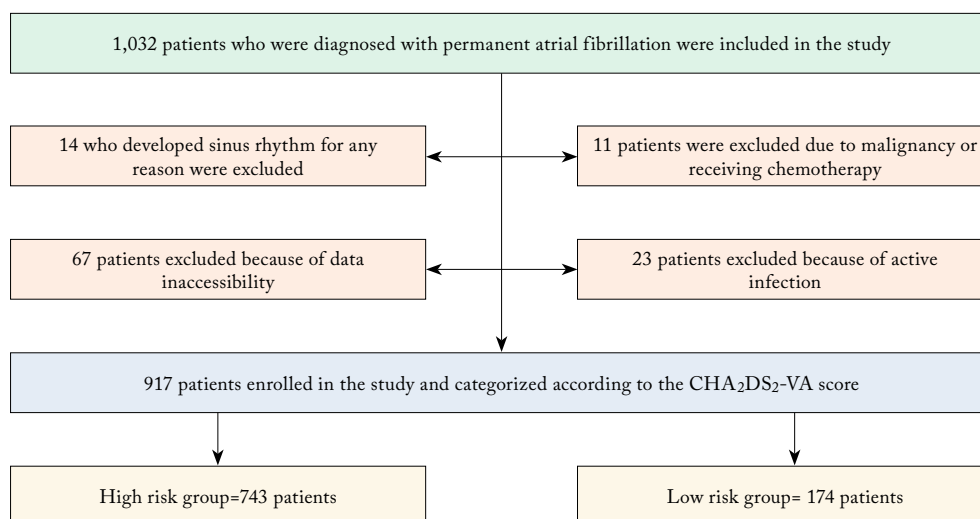
In the final European Society of Cardiology (ESC) consensus, the sex component was removed from the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and this score was renamed CHA<sub>2</sub>DS<sub>2</sub>-VA. In the present study, we aimed to investigate the prognostic value of the CHA<sub>2</sub>DS<sub>2</sub>-VA score newly defined by the ESC in patients with permanent AF.

## PATIENTS AND METHODS

This single-center, retrospective study was conducted at University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Department of Cardiology between January 2023 and June 2023. All patients over the age of 18 who were admitted to our clinic and diagnosed with permanent AF were included in the study. Initially, a total of 1,032 patients were reviewed. Patients who were restored to sinus rhythm for any reason (n=14), patients whose data were inaccessible (n=67), patients with active infection (n=23), and patients

with malignancy or receiving chemotherapy (n=11) were excluded from the study. Finally, a total of 917 patients (446 males, 471 females; mean age: 70.2±9.7 years; range, 27 to 89 years) who met the inclusion criteria were recruited. The study flowchart is shown in Figure 1. A written informed consent was obtained from each patient. The study protocol was approved by the University of Health Sciences, Gazi Yaşargil Training and Research Hospital (No: 275-12/12/2024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic and echocardiographic characteristics of the patients, oral anticoagulation drug regimens, and one-year follow-up results were evaluated. Stroke risk was calculated using the CHA<sub>2</sub>DS<sub>2</sub>-VA score, while bleeding risk was calculated using the HAS-BLED score (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly), when applicable. The patients were, then, divided into two groups according to the CHA<sub>2</sub>DS<sub>2</sub>-VA scores newly defined by the ESC.<sup>[14]</sup> Patients with a CHA<sub>2</sub>DS<sub>2</sub>-VA score ≥2 were included in the high-risk group (n=743), and those with a CHA<sub>2</sub>DS<sub>2</sub>-VA score <2 were included in the low-risk group (n=174). Follow-up data were collected by telephone interviews or clinic visits. The primary outcome measure was one-year all-cause mortality.



**Figure 1.** Study flowchart.

## Definitions

Systolic blood pressure (SBP)  $\geq 140$  mmHg, diastolic blood pressure (DBP)  $\geq 90$  mmHg, or the use of antihypertensive medication were considered as hypertension (HT). A fasting blood glucose level of  $\geq 126$  mg/dL, the use of anti-diabetic drugs, or a glycosylated hemoglobin (HbA1c) result in higher than 7% were considered diabetes mellitus (DM). Current smoking was the definition of smoking. The INR levels were measured at each center's local laboratory. The Cockcroft-Gault formula was used to determine glomerular filtration rates.<sup>[15]</sup> Glomerular filtration rate (GFR)  $< 60$  mL/min/1.73 m<sup>2</sup> or signs of kidney damage, or both, for a minimum of three months was considered chronic kidney disease (CKD).

The CHA<sub>2</sub>DS<sub>2</sub>-VA score was calculated according to the criteria published by the ESC in the latest guideline. The CHA<sub>2</sub>DS<sub>2</sub>-VA ranges from 0 to 8 (ESC). While calculating the CHADS<sub>2</sub>-VA score, 1 point is given for ages 65-74, 1 point for heart failure, 1 point for HT, 1 point for DM, 1 point for a history of vascular disease, 2 points for age 75 and over, and 2 points for the history of stroke, transient ischemic attack, or systemic thromboembolism.<sup>[13]</sup>

## Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 27.0 software (IBM Corp., Armonk, NY, USA). The normal distribution of variables was analyzed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were expressed in mean  $\pm$  standard deviation (SD) or median (interquartile range), while categorical variables were expressed in number and frequency. Depending on the distributions, the Mann-Whitney U test or Student t-test were used to compare continuous variables. For continuous variables, univariate analysis was used, while the chi-square or Fisher exact test was utilized for categorical variables. The association between survival and CHA<sub>2</sub>DS<sub>2</sub>-VA score over a 12-month follow-up period was examined using the Kaplan-Meier test. The variables influencing mortality for one-year were assessed using univariate Cox regression analysis. Parameters with a *p* value of  $< 0.05$  in the univariate Cox regression analyses were included in the multivariate Cox regression analyses. A *p* value of  $< 0.05$  was considered statistically significant.

## RESULTS

In this study, patients with a CHA<sub>2</sub>DS<sub>2</sub>-VA score of  $\geq 2$  were included in the high-risk group (n=743), and patients with a CHA<sub>2</sub>DS<sub>2</sub>-VA score of  $< 2$  were included in the low-risk group (n=174). No significant difference was observed between the groups in terms of body mass index (BMI), heart rate, smoking, hemoglobin, platelet, and albumin ( $p < 0.05$  for all).

Mean age (71.9 $\pm$ 9 *vs.* 62.8 $\pm$ 8.8 years,  $p < 0.001$ ), CHA<sub>2</sub>DS<sub>2</sub>-VA score (3.12 $\pm$ 1.16 *vs.* 0.75 $\pm$ 0.43,  $p < 0.001$ ), SBP (129 $\pm$ 17.6 *vs.* 125.9 $\pm$ 16.9 mmHg,  $p = 0.035$ ), DBP (78.3 $\pm$ 11.6 *vs.* 75.2 $\pm$ 11.1 mmHg,  $p = 0.002$ ), and HAS-BLED score (2 [1] *vs.* 1 [1],  $p < 0.001$ ) were higher in the high-risk group. Additionally, as expected, the number of patients with HT (539 [72.5] *vs.* 76 [43.7],  $p < 0.001$ ), DM (174 [23.4] *vs.* 13 [7.5],  $p < 0.001$ ), ischemic cerebrovascular disease (CVD) (57 [7.7] *vs.* 4 [2.3],  $p = 0.010$ ), hemorrhagic CVD (4 [0.5] *vs.* 2 [1.1],  $p = 0.368$ ), chronic obstructive pulmonary disease (COPD) (147 [19.8] *vs.* 24 [13.8],  $p = 0.040$ ), CKD (556 [74.8] *vs.* 110 [63.2],  $p = 0.002$ ), heart failure with reduced ejection fraction (HFrEF) (209 [28.1] *vs.* 17 [9.8],  $p < 0.001$ ) and one-year mortality rates (69 [9.3] *vs.* 4 [2.3],  $p = 0.002$ ) were higher in the high-risk group. Also, the mean left ventricular ejection fraction (LVEF) (49.9 $\pm$ 10.8 *vs.* 54.5 $\pm$ 8.6%,  $p < 0.001$ ) and GFR (39.1 [33] *vs.* 52.4 [43] mL/min/1.73 m<sup>2</sup>,  $p < 0.001$ ) were statistically significantly lower in the high-risk group (Table 1).

Univariate Cox regression analyses were performed to investigate predictors of one-year all-cause mortality. In these analyses, CHA<sub>2</sub>DS<sub>2</sub>-VA score (hazard ratio [HR]=1.368, 95% confidence interval [CI]: 1.180-1.585,  $p < 0.001$ ), age (HR=1.057, 95% CI: 1.029-1.086,  $p < 0.001$ ), female sex (HR=3.630, 95% CI: 2.109-6.246,  $p < 0.001$ ), SBP (HR=0.982, 95% CI: 0.968-0.996,  $p = 0.009$ ), LVEF (HR=0.961, 95% CI: 0.941-0.981,  $p < 0.001$ ), COPD (HR=1.972, 95% CI: 1.196-3.251,  $p = 0.008$ ), CKD (HR=1.792, 95% CI: 1.004-3.215,  $p = 0.014$ ), hemoglobin (HR=0.867, 95% CI: 0.772-0.973,  $p = 0.015$ ), neutrophil (HR=1.060, 95% CI: 1.036-1.085,  $p < 0.001$ ), and lymphocyte (HR=0.930, 95% CI: 0.930-0.957,  $p < 0.001$ ) were statistically significant predictors of one-year all-cause mortality (Table 2).

**Table 1**  
Baseline characteristics of total population

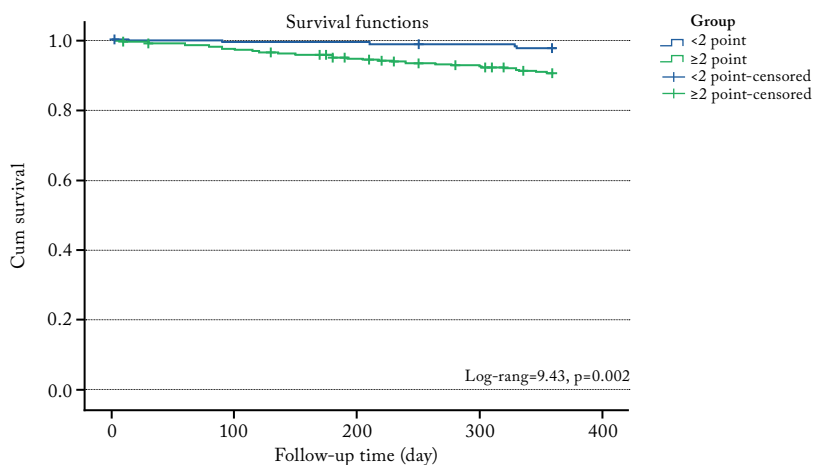
Parameters	High risk group			Low risk group			Total			p		
	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median		IQR	
Age (year)			71.9±9					70.2±9.7			<0.001	
Sex											<0.001	
Female	351	47.2				120	69			471	51.4	
CHA <sub>2</sub> DS <sub>2</sub> -VA score			3.12±1.16					0.75±0.43				<0.001
Body mass index (kg/m <sup>2</sup> )			28.3±3.8					28±3.9				0.410
Heart rate (min)			88.6±17.5					88±18.5				0.696
Systolic blood pressure (mmHg)			129±17.6					125.9±16.9				0.035
Diastolic blood pressure (mmHg)			78.3±11.6					75.2±11.1				0.002
LVEF (%)			49.9±10.8					54.5±8.6				<0.001
GFR (mL/min)-IQR				39.1	33			52.4	43	41.4	35	<0.001
HAS-BLED score-IQR				2	1			1	1	2	1	<0.001
Hemoglobin (g/dL)			13±2					13.2±1.9				0.318
Platelet (10 <sup>3</sup> /μL)			230.7±72					232.1±64.5				0.812
Neutrophile (10 <sup>3</sup> /μL)			64.2±9.8					60.1±9.7				<0.001
Lymphocyte (10 <sup>3</sup> /μL)			24.7±8.7					28±9.4				<0.001
Glucose (mg/dL)			120.6±41.7					105.8±23				<0.001
Urea (mg/dL)			34.3±15.4					28.1±13.5				<0.001
Creatinin (mg/dL)-IQR				0.9	0.41			0.8	0.23	0.9	0.34	<0.001
Albumin (g/dL)			4.06±0.52					4.05±0.49				0.873
Total cholesterol (mg/dL)			174.9±42					181.1±44				0.043
HFrEF	209	28.1				17	9.8			226	24.6	<0.001
CKD	556	74.8				110	63.2			666	72.6	0.002
Smoker	118	15.9				24	13.8			142	15.5	0.493
Hypertension	539	72.5				76	43.7			615	67.1	<0.001
Diabetes mellitus	174	23.4				13	7.5			187	20.4	<0.001
Ischemic CVD/TIA	57	7.7				4	2.3			61	6.7	0.010
Hemorrhagic CVD	4	0.5				2	1.1			6	0.7	0.368
COPD	147	19.8				24	13.8			171	18.6	0.040
One-year mortality	69	9.3				4	2.3			73	8	0.002

SD: Standard deviation; IQR: Interquartile range; LVEF: Left ventricular ejection fraction; GFR: Glomerular filtration rate; CKD: Chronic kidney disease; CVD: Cerebrovascular disease; TIA: Transient ischemic attack; COPD: Chronic obstructive pulmonary disease. Low risk group; patients with a CHA<sub>2</sub>DS<sub>2</sub>-VA score <2; High risk group; patients with a CHA<sub>2</sub>DS<sub>2</sub>-VA score ≥2; P value of <0.05 shows statistical significance.

**Table 2**  
Cox Regression analysis of 1-year all-cause mortality

Parameters	Univariable			Multivariable		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
CHA <sub>2</sub> DS <sub>2</sub> -VA score	1.368	1.180-1.585	<b>&lt;0.001</b>	1.040	0.863-1.254	0.679
Age	1.057	1.029-1.086	<b>&lt;0.001</b>	1.035	1.005-1.065	<b>0.022</b>
Sex / Female	3.630	2.109-6.246	<b>&lt;0.001</b>	2.978	1.662-5.337	<b>&lt;0.001</b>
Body mass index	0.949	0.892-1.009	0.092			
Heart rate	0.992	0.979-1.006	0.255			
Systolic blood pressure	0.982	0.968-0.996	<b>0.009</b>	0.984	0.970-0.997	<b>0.019</b>
LVEF	0.961	0.941-0.981	<b>&lt;0.001</b>	0.977	0.954-1.000	<b>0.047</b>
COPD	1.972	1.196-3.251	<b>0.008</b>	1.759	1.040-2.974	<b>0.035</b>
CKD	1.792	1.004-3.215	<b>0.014</b>	1.133	0.607-2.112	0.695
Smoking	2.208	0.585-7.279	0.154			
Hypertension	1.072	0.654-1.756	0.783			
Diabetes mellitus	1.294	0.760-2.204	0.342			
Ischemic CVD/TIA	1.280	0.555-2.951	0.562			
Hemoglobin	0.867	0.772-0.973	<b>0.015</b>	0.870	0.774-0.978	<b>0.019</b>
Glucose	0.999	0.992-1.005	0.638			
Platelet	1.000	0.996-1.003	0.786			
Neutrophile	1.060	1.036-1.085	<b>&lt;0.001</b>	1.033	0.995-1.072	0.091
Lymphocyte	0.930	0.930-0.957	<b>&lt;0.001</b>	0.989	0.943-1.036	0.632
Albumin	0.853	0.550-1.323	0.477			

HR: Hazard ratio; CI: Confidence interval; LVEF: Left ventricular ejection fraction; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CVD: Cerebrovascular disease; TIA: Transient ischemic attack.



**Figure 2.** Kaplan-Meier analysis of relationship between CHA<sub>2</sub>DS<sub>2</sub>-VA score and 1-year all-cause mortality.

In the multivariate Cox regression analyses, only age (HR=1.035, 95% CI: 1.005-1.065,  $p=0.022$ ), female sex (HR=2.978, 95% CI: 1.662-5.337,  $p<0.001$ ), SBP (HR=0.984, 95% CI: 0.970-0.997,  $p=0.019$ ), COPD (HR=1.759, 95% CI: 1.040-2.974,  $p=0.035$ ), LVEF (HR=0.977, 95% CI: 0.954-1.000,  $p=0.047$ ), and hemoglobin (HR=0.870, 95% CI: 0.774-0.978,  $p=0.019$ ) were found to be independent predictors (Table 2).

The Kaplan-Meier analysis was performed to identify the relationship between CHA<sub>2</sub>DS<sub>2</sub>-VA score and one-year all-cause mortality. As a result of the analysis, the relationship between CHA<sub>2</sub>DS<sub>2</sub>-VA score and one-year all-cause mortality was statistically significant (log-rank=9.43,  $p=0.002$ ) (Figure 2).

## DISCUSSION

In the current study, we investigated the effect of CHA<sub>2</sub>DS<sub>2</sub>-VA score on one-year all-cause mortality in patients with permanent AF. Our study results showed a statistically significant relationship between the CHA<sub>2</sub>DS<sub>2</sub>-VA score and one-year mortality. However, the CHA<sub>2</sub>DS<sub>2</sub>-VA score was not an independent predictor of one-year all-cause mortality in patients with permanent AF. In addition, age, LVEF, COPD, female sex, hemoglobin level, and SBP were independent predictors of one-year all-cause mortality in permanent AF patients.

In previous studies investigating AF prognosis, results regarding the effect of sex are confusing. In the study by Dagues et al.,<sup>[16]</sup> male patients were more likely to have CAD and idiopathic AF, whereas female patients were older and more likely to have DM, thyroid disease, valvular heart disease, and HT. Overall, women were more likely than males to have comorbidities, be at the highest risk for stroke, and had symptoms. Other long-term morbidities and mortality rates were similar. The results from the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) study, which included over 28,000 patients, showed that the unadjusted rate of all-cause mortality was only slightly higher in women than in men and, after adjustment for baseline risk factors, the rate of all-cause mortality was similar between women and men.<sup>[17]</sup> According to Emdin et al.'s<sup>[18]</sup> meta-analysis of more than 4,000,000 patients, women with

AF had a greater relative risk of heart failure, cardiovascular death, stroke, all-cause mortality, and cardiac events than males.<sup>[18]</sup> In our study, similar results were found in the meta-analysis study conducted by Emdin et al.<sup>[18]</sup> in female AF patients. However, the effect of sex on mortality in AF patients is debatable. Many studies have shown that female patients have more comorbidities, more suffer from obesity, and are older patients. The outcomes of the female sex are expected to be worse, although its effect on mortality is still unclear.

According to Goldhaber et al.,<sup>[19]</sup> compared to patients under 65 years of age, the HRs for major adverse clinical outcomes within 24 months of follow-up for overall mortality, cardiovascular and non-cardiovascular mortality, non-hemorrhagic stroke or systemic embolism, major bleeding, myocardial infarction/acute coronary syndrome, and new or worsening heart failure increased with older age category. Many comorbidities and frailties are expected in older patients. It is not surprising that many diseases are predictors of mortality in this patient group. In our study, similar to previous studies,<sup>[19,20]</sup> age was an independent predictor of one-year mortality.

Previous studies have demonstrated that anemia is associated with poor prognosis and death in patients with AF.<sup>[21,22]</sup> Anemia was revealed to be an independent predictor of major adverse cardiac and cerebrovascular events as well as all-cause mortality by the Atrial Fibrillation Undergoing Coronary Stenting (AFCAS) registry.<sup>[22]</sup> Additionally, compared to AF patients who were not anemic, anemia was linked to a considerably higher risk of severe bleeding events, stroke, thromboembolic events, and all-cause death, according to the Danish registry.<sup>[21]</sup> In our study, in line with these studies, low hemoglobin level was an independent predictor of one-year all-cause mortality.

Heart failure has also been shown to increase one-year mortality in patients with AF in previous studies. A significant relationship was demonstrated between heart failure and mortality in the study conducted by Fauchier et al.<sup>[1]</sup> The Randomized Evaluation of Long-term Anticoagulant Therapy: dabigatran vs. warfarin (RELY-AF) study<sup>[23]</sup> and XANTUS (Xarelto® for Prevention of Stroke in Patients with Atrial Fibrillation)<sup>[24]</sup> real-life data also showed that heart failure was associated with



one-year all-cause mortality in patients with AF. The difference between our study and these studies is the mortality rate in patients. In our study, the one-year all-cause mortality rate was 8% and the mortality rate was higher compared to other studies. We believe that the reason for this is that we only included permanent AF patients in our study. Permanent AF is seen in more frail and older patients than other types of AF, and worse clinical outcomes are expected in permanent AF.

In Denmark, an observational study examined whether death rates differed for patients with AF and COPD based on the order of diagnosis.<sup>[25]</sup> After five years, more than half of these patients died, showing poor prognosis. Patients diagnosed with AF before COPD had a 26% lower death risk than those with COPD diagnosed first. Earlier COPD diagnosis increased mortality risk. In the meta-analysis study by Ye et al.,<sup>[26]</sup> AF patients with COPD were found to be associated with increased overall mortality, increased cardiovascular mortality, and more frequent bleeding complications compared to AF patients without COPD. Our study found similar results to previous studies. Taken together, it should be kept in mind that COPD is a risk factor in predicting mortality, given the fact that it is frequently seen in AF patients.

Nonetheless, there are some limitations to this study. First, this study is a single-center and retrospective study. Therefore, the results cannot be generalized. Second, since our study is retrospective, some bias could not have been completely eliminated. Third, in the multivariate analyses, some other parameters could have been included; however, we have missing data. Finally, we have no data on hemorrhagic or ischemic CVD that developed during follow-up in the patients, and since we are unaware of the causes of death, only predictors of all-cause death were analyzed.

In conclusion, our study results showed that the CHA<sub>2</sub>DS<sub>2</sub>-VA score was associated with one-year all-cause mortality in AF patients, but it was not an independent predictor when evaluated with all parameters affecting mortality. In the management of AF patients, the CHA<sub>2</sub>DS<sub>2</sub>-VA score may be useful not only in determining oral anticoagulation strategy, but also in the approach of clinicians to AF patients, considering that it may be a predictor of mortality.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** All authors contributed equally to this article.

**Conflict of Interest:** The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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