CHA_2DS_2-VASc Score Predicts Adverse Outcome in Patients with Simple Congenital Heart Disease Regardless of Cardiac Rhythm

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Abstract

Adult patients with simple congenital heart disease (sACHD) represent an expanding population vulnerable to atrial arrhythmias (AA). CHA_2DS_2-VASc score estimates thromboembolic risk in non-valvular atrial fibrillation patients. We investigated the prognostic role of CHA_2DS_2-VASc score in a non-selected sACHD population regardless of cardiac rhythm. Between November 2009 and June 2018, 427 sACHD patients (377 in sinus rhythm, 50 in AA) were consecutively referred to our ACHD service. Cardiovascular hospitalization and/or all-cause death were considered as composite primary end-point. Patients were divided into group A with CHA_2DS_2-VASc score = 0 or 1 point, and group B with a score greater than 1 point. Group B included 197 patients (46%) who were older with larger prevalence of cardiovascular risk factors than group A. During a mean follow-up of 70 months (IQR 40–93), primary end-point occurred in 94 patients (22%): 72 (37%) in group B and 22 (10%, $p < 0.001$) in group A. Rate of death for all causes was also significantly higher in the group B than A (22% vs 2%, respectively, $p < 0.001$). Multivariable Cox regression analysis revealed that CHA_2DS_2-VASc score was independently related to the primary end-point (HR 1.84 [1.22–2.77], $p = 0.004$) together with retrospective AA, stroke/TIA/peripheral thromboembolism and diabetes. Furthermore, CHA_2DS_2-VASc score independently predicted primary end-point in the large subgroup of 377 patients with sinus rhythm (HR 2.79 [1.54–5.07], $p = 0.01$). In conclusion, CHA_2DS_2-VASc score accurately stratifies sACHD patients with different risk for adverse clinical events in the long term regardless of cardiac rhythm.

Keywords Congenital heart disease · CHA_2DS_2-VASc score · Cardiac rhythm · Heart failure

The number of adults with congenital heart disease continues to increase [1, 2], the majority experiencing simple defects with excellent prognosis and easy clinical management [3, 4], thus current international guidelines do not suggest regular follow-up [1]. However, there is a discrepancy in the results of a number studies which report conflicting data about mortality and morbidity rates in these adult patients with simple congenital heart disease (sACHD) [3–6] who are vulnerable to atrial arrhythmias (AA) due to previous volume or pressure overload and surgical scars [7–9]. The CHA_2DS_2-VASc score is currently used to estimate the risk of stroke/transient ischaemic attack (TIA) and peripheral thromboembolism (TE) in patients with non-valvular atrial fibrillation (NVAF) and to guide the anticoagulant treatment in clinical practice [10, 11]. CHA_2DS_2 stands for (Congestive heart failure, Hypertension, Age ($> 65 = 1$ point, $> 75 = 2$ points), Diabetes, previous Stroke/transient ischemic attack (2 points). VASc stands for vascular disease (peripheral arterial disease, previous myocardial infarction, aortic atheroma), and Sex category (female gender). A patient's annual stroke risk rises in line with the increase of this score. Patients with atrial fibrillation and CHA_2DS_2-VASc ≥ 2 present a moderate to high risk of thromboembolic events and require anticoagulation treatment, while patients with a score < 1 have a very low risk and do not require this treatment. A score of 1 corresponds to low risk and the use of anticoagulant therapy is debatable [10].

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Recently, the CHA_2DS_2-VASc score has been successfully tested in populations with sinus rhythm and high risk of cardiovascular (CV) events [12–15]. Its role is still unclear in the ACHD population and it has never been applied to a population consisting exclusively of sACHD.

Our study aimed at assessing whether the CHA_2DS_2-VASc score can predict adverse clinical outcomes in sACHD patients and if its use can eventually be extended to sACHD patients with no history of atrial arrhythmias.

Methods

In November 2009, an outpatient clinic dedicated to this category of patients was opened in the Cardiology Department of the Integrated Health Service of the University of Trieste, allowing us to record medical, clinical, and cardiac imaging data of 427 consecutive adults, until June 2018. Retrospective data and data gathered during the follow-up were recorded in the patient's e-chart (Cardionet, Insiel) and then subsequently migrated to the regional health data warehouse. At the time of the enrollment, the cardiologists of the Cardiovascular Center collected and validated surgical repairs, intervention documents, previous hospitalizations, and emergency room admissions, as useful variables for the calculation of the CHA_2DS_2-VASc risk score.

The hospitalizations were classified according to the International Classification of Disease 9 (ICD-9 CM) codes of hospital discharge reports, and the vital status were extracted from the regional register of births and deaths. The regional health data warehouse updated all information monthly. Each patient signed informed consent, and the study protocol complied with ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The present study included, in patients with sACHD, those subjects with an isolated and uncomplicated diagnosis of the atrial septal defect, interventricular septal defect, with normal pulmonary vascular resistance, patent ductus arteriosus, mild or moderate pulmonary valve stenosis or bicuspid aortic valve (without severe regurgitation). Patients with a combination of simple congenital heart disease or more complex cardiac diseases and any childhood comorbidity, such as genetic syndromes, mental, kidney, gastrointestinal, and pulmonary disease were excluded. Patients with patent foramen ovale, moderate-to-severe mitral stenosis, and mechanical prosthetic valves were also excluded [10]. We included all the following AA: paroxysmal, persistent, or permanent atrial fibrillation, atrial flutter, atrial tachycardia and collected data related to risk factors for coronary artery disease, clinical characteristics, laboratory values, hospital course, demographic characteristics, and medical history. The ischemic stroke was defined as a focal neurological deficit of sudden onset as diagnosed by a neurologist, lasting more than 24 h and caused by ischemia. The TIA was categorized as a focal neurological deficit of sudden onset and diagnosed by a neurologist, lasting less than 24 h. Finally, the peripheral TE was defined by the responsible physician as the occlusion of blood flow by an embolus, outside the brain and heart [16]. The pre-specified primary end-point of the study was a composite of all causes of death and major adverse cardiovascular events (MACE) requiring hospitalization including cardiac events (unstable angina, myocardial infarction, non-myocardial infarction, acute coronary syndrome, HF, percutaneous coronary intervention, and coronary artery bypass grafting), and vascular events (stroke, TIA, TE, peripheral vascular intervention, and stent thrombosis). For each patient, the follow up was stopped at the time of the first MACE or death. We classified the hospitalizations according to the International Classification of Disease 9 (ICD-9 CM) codes derived from the hospital discharge reports, and extracted the state of being, alive or deceased, from the regional register of births and deaths. Follow-up ended with the data extraction on the 30th June 2018. Data were reported as mean values $\pm$ 1 standard deviation (mean and interquartile ranges for variables deviating from normality) or percentages. We used unpaired Student's test and χ^2 statistics for descriptive statistics. We performed between group comparisons of categorical and continuous variables by χ^2 test and analysis of variance (ANOVA) and compared each group by Scheffè test for unequal sample, or Mann–Whitney non-parametrical test. Log cumulative hazard functions were computed by univariable and multivariable Cox regression to identify the factors independently associated with the study of the clinical end-point. The multivariable model included variables significantly related to the study end-point in the univariable tests ($p \leq 0.10$). Based on the results of the ROC curves analysis (see below), the CHA_2DS_2-VASc risk score was tested both as continuous and as a dichotomic variable (0–1 point vs. > 1 point). Sensitivity, specificity, and predictive accuracy of the independent predictors of the study end-point were analyzed by specific receiver operating characteristic (ROC) curve analyses. We compared the ROC curve resulting from the CHA_2DS_2-VASc risk score, AA, diabetes, and previous ischaemic stroke/transient ischemic attack/peripheral thromboembolism (TE) for the primary end-point, using the z statistics. Probabilities of event-free survival and Kaplan–Meier survival curves of patients with CHA_2DS_2-VASc risk score 0–1 vs. those with score > 1 were detected (differences between the curves were tested for significance by the Log-rank test). We performed a sub-analysis in a large group of patients in sinus rhythm, excluding 50 patients with AA, using the statistical package SPSS 19.0 (SPSS Inc. Chicago. Illinois) and identifying statistical significance by two-tailed $p < 0.05$.

Results

The study population consisted of 427 consecutive patients (average age 53 years, IQR 37–68, 43% women), 43% suffered from arterial hypertension, 13% had a history of heart failure, 8% previous stroke/TIA/TE while 50 patients (12%) presented AA at the time of enrollment. Patients with AA and sinus rhythm had similar clinical characteristics except for age (mean 61 [57–75] vs 57 [35–67], $p < 0.001$) and the prevalence of the CHA_2DS_2-VASc score > 1 (64% vs 44%, $p = 0.02$) that appeared older and higher, respectively, in patients with AA. The baseline clinical characteristics of the whole study population are shown in Table 1.

We divided the study population according to the CHA_2DS_2-VASc score into two groups: group A including patients with score = 0 or 1 point, and group B, including patients with a score higher than 1 point, whose baseline clinical features are listed and compared in Table 1. Group B included 197 patients (46% of the total study population) who were older, with higher CV risk factors and a more frequent history of HF, chronic renal failure, ischemic vascular events, and AA compared to the 230 patients belonging to group A. Overall the former received beta-blockers, ACEi/ARBs, diuretics, antiarrhythmic drugs and anticoagulant agents more frequently than the latter. Data on vital status

Table 1 Baseline characteristics of the study population divided in two subgroups according to the CHA_2DS_2-VASc score

Variables	Group A CHA_2DS_2-VASc 0–1 (230 pts)	Group B CHA_2DS_2-VASc > 1 (197 pts)	*p*	Total study population (427 pts)
Demographics				
Age in year (IQR)	41 [IQR 29–75]	69 [IQR 61–74]	< 0.001	53 [IQR 37–68]
Female gender (n, %)	71 (31%)	112 (57%)	< 0.001	183 (43%)
Systolic blood pressure (mmHg)	125 ± 5	130 ± 12	< 0.001	130 ± 10
Comorbidities				
Smoke (n, %)	42 (18%)	41 (21%)	0.75	83 (19%)
Hypertension (n, %)	39 (17%)	144 (73%)	< 0.001	183 (43%)
Dyslipidemia (n, %)	39 (17%)	93 (47%)	< 0.001	132 (31%)
Diabetes Mellitus (n, %)	1 (1%)	41 (21%)	< 0.001	42 (10%)
COPD	5 (2%)	30(15%)	< 0.001	35 (8%)
Ischemic Heart Disease (n, %)	6 (3%)	54 (27%)	< 0.001	60 (14%)
Chronic Renal Disease (n, %)	2 (1%)	29 (15%)	< 0.001	31 (7%)
History of heart failure (n, %)	4 (2%)	53 (27%)	< 0.001	57 (13%)
Atrial Arrhythmia	18 (8%)	32 (16%)	0.007	50 (12%)
Infective Endocarditis	11 (5%)	1 (1%)	0.008	12 (3%)
Ischaemic stroke/TIA/TE (n, %)	0 (0%)	36 (18%)	< 0.001	36 (8%)
LVEF < 50% (n,%)	7 (4%)	8 (6%)	0.44	15 (5%)
Implantable pace maker (n, %)	4 (2%)	18 (9%)	0.001	22 (5%)
ICD (n, %)	1 (1%)	3 (1%)	0.41	4 (0.9%)
Medications				
ACEi/ARBs (n, %)	44 (19%)	120 (61%)	< 0.001	164 (38%)
Betablockers (n, %)	51 (22%)	77 (39%)	< 0.001	128 (30%)
Diuretics (n, %)	13 (6%)	103 (52%)	< 0.001	116 (27%)
Calcium antagonists (%)	1 (1%)	8 (4%)	0.009	9 (2%)
Statins (n, %)	17 (7%)	74 (38%)	< 0.001	91 (21%)
Aldosterone Antagonists (n, %)	3 (1%)	35 (18%)	< 0.001	38 (9%)
Antiarrhythmic drugs (n, %)	19 (8%)	30 (15%)	0.02	49 (11%)
Digoxin (n, %)	3 (1%)	15 (8%)	0.001	18 (4%)
Anti-platelets agents (n, %)	23 (10%)	50 (25%)	< 0.001	73 (17%)
Anticoagulant agents (n, %)	24 (10%)	53 (27%)	< 0.001	77 (18%)

ACEi angiotensin-converting enzyme inhibitors; Antiarrhythmic drugs Flecainide or Propafenone or Sotalol or Amiodarone; *ARB* angiotensin T1 receptor blockers; *COPD* chronic obstructive pulmonary disease; *LVEF* left ventricular ejection fraction; *ICD* implantable cardioverter defibrillator; *TE* thromboembolism; *TIA* transient ischemic attack

and MACE were available for all patients. During a mean follow-up of 70 months (IQR 40–93), a primary end-point (all-cause death or MACE) occurred in 94 patients (22%): CV death as first event in 8 patients, non-CV death as first event in 8 patients, cardiac event requiring hospitalization in 49 patients and vascular event requiring hospitalization in 37 patients. Forty-eight patients (11%) died during the follow-up, and 40 of them experienced a MACE, which required hospitalization before dying. Among the 49 patients (13%) who had a cardiac event, 26 underwent coronary bypass grafting, while among the 37 patients (8%) who had a vascular event, 8 underwent vascular surgery. Table 2 shows the event rate according to the CHA_2DS_2-VASc score (dichotomized in 0–1 vs > 1 point). The primary end-point occurred more frequently in group B than A (37% vs 10%, respectively; $p < 0.001$), and even if considered separately, both cardiac and vascular events occurred more frequently in the former. The rate of death for all causes was also significantly higher in the group B than in A (43 patients = 22% vs 5 patients = 2%; $p < 0.001$, respectively). At univariable Cox regression, the variables associated with the primary study end-point were older age, female gender, hypertension, diabetes, AA, ischemic heart disease, previous stroke/TIA/TE, chronic renal dysfunction, lower hemoglobin, history of heart failure, and CHA_2DS_2-VASc score (used both as continuous and dichotomized variable). Multivariable Cox regression revealed that the CHA_2DS_2-VASc score (used as a dichotomized variable) was independently related to the primary end-point together with previous stroke/TIA/TE, diabetes, and AA (Table 3). ROC curves showed that the CHA_2DS_2-VASc score had the best (and significantly higher) predictive accuracy for primary end-point among the

Table 2 Death for all causes and MACE (cardiac and vascular events) during follow up, according to the CHA_2DS_2-VASc score at the baseline evaluation

Variables	Group A CHA_2DS_2-VASc 0–1 (230 pts)	Group B CHA_2DS_2-VASc > 1 (197 pts)	*P*	Total events (427 pts)
Composite end-point (n, %)	22 (10%)	72 (37%)	< 0.001	94 (22%)
Cardiac events (n, %)	17 (7%)	32 (16%)	< 0.001	49 (11%)
No CABG	9 (4%)	14 (7%)	0.18	23 (5%)
CABG	8 (3%)	18 (9%)	0.008	26 (6%)
Stroke, TIA, TE events (n, %)	3 (1%)	34 (17%)	< 0.001	37 (8%)
No vascular surgery	2 (1%)	27 (14%)	< 0.001	29 (7%)
Vascular surgery	1 (0.4%)	7 (4%)	0.005	8 (2%)
Cardiovascular death as first event (n, %)	2 (1%)	6 (3%)	< 0.001	8 (2%)
Non cardiovascular death as first event (n, %)	2 (1%)	6 (3%)	< 0.001	8 (2%)
All-causes death (n, %)	5 (2%)	43 (22%)	< 0.001	48 (11%)

CABG coronary artery bypass graft, *TE* thromboembolism, *TIA* transient ischemic attack

Table 3 Variables associated with the primary study end-point: univariable and multivariable Cox regression analyses

Univariate analysis						Multivariate analysis		
	Endpoint NO (333 pts)	Endpoint YES (94 pts)	HR	CI	*p*	HR	CI	*p*
Age (years)	54 ± 18	71 ± 14	1.05	1.03 – 1.06	< 0.001	1.02	0.98 – 1.04	0.66
Female gender (%)	40	51	1.43	1.00 – 2.14	0.049	1.55	0.86 – 2.90	0.14
Hypertension (%)	37	65	2.57	1.68 – 3.92	< 0.001	1.17	0.59 – 2.2	0.73
Diabetes mellitus (%)	19	43	2.36	1.41 – 3.95	0.001	2.90	1.24 – 6.75	0.01
Chronic renal disease (%)	4	19	3.39	2.02 – 5.67	< 0.001	1.14	0.58 – 2.28	0.55
Hemoglobin (g/dl)	13.1 ± 3.5	11.3 ± 3.8	0.89	0.83 – 0.94	< 0.001	0.94	0.87 – 1.01	0.07
Ischemic heart disease (%)	10	28	1.43	1.31 – 1.56	< 0.001	1.65	0.90 – 3.06	0.11
Previous stroke/TIA/TE	7	14	1.75	1.00 – 3.20	0.048	4.42	1.48 – 13.20	0.008
Atrial Arrhthymia (%)	9	20	1.94	1.17 – 3.21	0.006	1.94	1.11 – 3.38	0.02
History of heart failure (%)	8	34	3.84	2.50 – 5.88	< 0.001	1.21	0.60 – 2.41	0.59
CHA_2DS_2-VASc (mean ± SD)	1.47 ± 1.2	3.11 ± 1.9	1.43	1.31 – 1.56	< 0.001			
CHA_2DS_2-VASc score (0–1 vs > 1)	10	37	4.28	2.65 – 6.90	< 0.001	1.84	1.22 – 2.77	0.004

TE thromboembolism; *TIA* transient ischemic attack

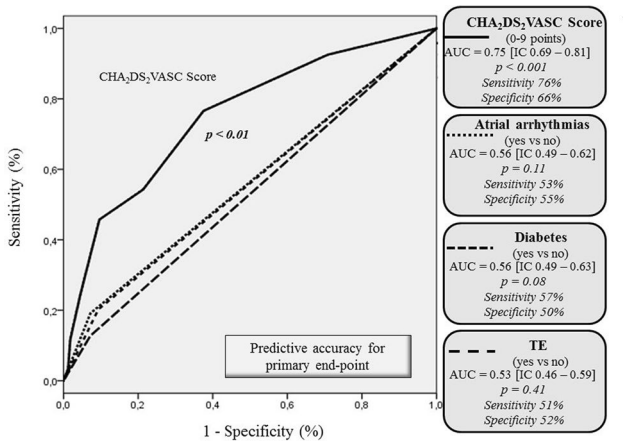

Fig. 1 Predictive accuracy of CHA_2DS_2-VASc score, Atrial arrhythmia, diabetes and previous ischaemic stroke/transient ischemic attack/peripheral thromboembolism (TE) for the primary end-point in the 427 study patients. *ROC* curve analysis. *AUC* area under the curve

other prognosticators of events (Fig. 1). The Kaplan–Meier survival curves for the primary end-point of patients with CHA_2DS_2-VASc risk score 0–1 vs. those with score > 1 are shown in Fig. 2 (left panel). We performed a sub-analysis dedicated to patients in sinus rhythm (377 subjects = 88% of the total study population). During the follow-up, group B showed a higher incidence of primary endpoints 35% vs. 8% (57 events / 165 patients vs 12 events / 212 patients, $p < 0.001$), when compared to group A. Both at univariable (HR 4.51 [2.66–7.68], $p < 0.001$) and multivariable analysis (HR 2.79 [1.54–5.07], $p = 0.01$), the CHA_2DS_2-VASc score independently predicted primary end-point together with history of HF (HR 2.80 [1.67–4.67], $p < 0.001$) and ischemic heart disease (HR 1.71 [1.01 – 2.96], $p = 0.04$). Kaplan–Meier survival curves for the primary end-point of patients in sinus rhythm with CHA_2DS_2-VASc risk score 0–1 point vs. those in sinus rhythm with score > 1 point are shown in Fig. 2 (right panel).

Discussion

The use of the CHA_2DS_2-VASc score is recommended to estimate the risk of stroke in NVAF patients according to the international guidelines [10, 11, 17]. Recently, it has been successfully tested as a predictor of adverse outcomes in populations with sinus rhythm and high risk of CV events [12–15], but it has never been applied in sACHD populations. Our study demonstrated three original and clinically relevant findings: (1) in sACHD patients, the CHA_2DS_2-VASc score is a reliable prognosis of long-term adverse outcomes, which shows good accuracy in predicting cardiovascular events and deaths from all causes; (2) in this population the CHA_2DS_2-VASc score predicts adverse outcome regardless of the previous AA, stroke/TIA/TE, diabetes and seems to be useful in the sACHD patients with

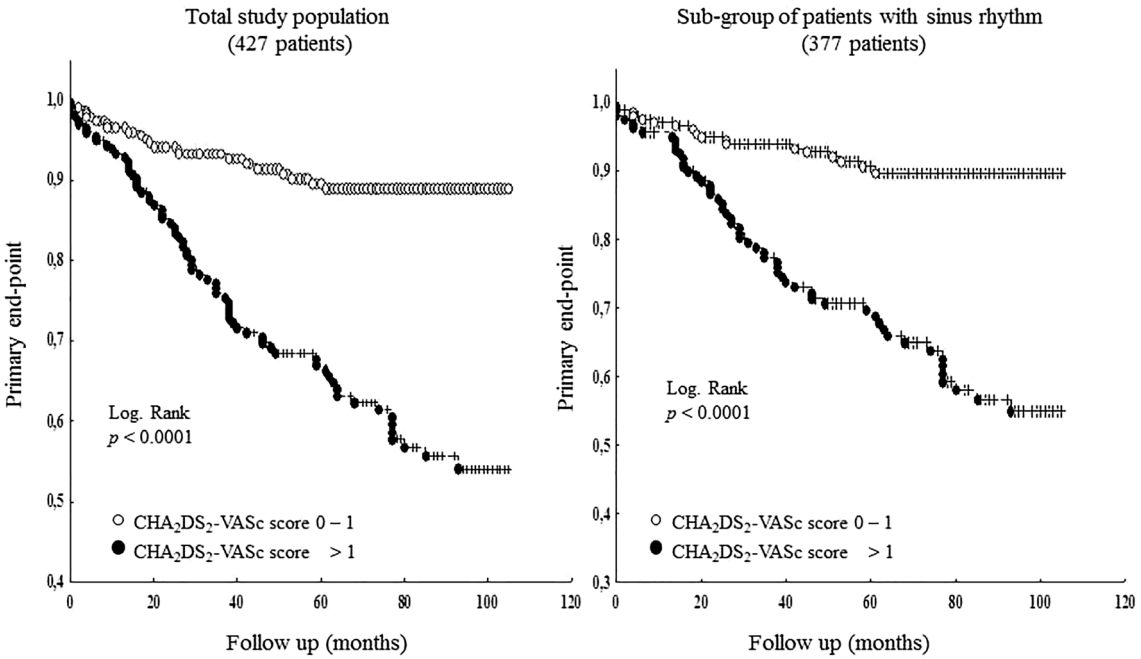

Fig. 2 Kaplan–Meier survival curves from primary end-point of patients with CHA_2DS_2-VASc risk score 0–1 point vs those with score > 1 point. Total study population (427 patients) were analyzed and showed in the left panel. Right panel refers to the subgroup of 377 patients in sinus rhythm (50 patients with NVAF at enrollment were excluded)

known sinus rhythm; (3) there is a prognostic cut-off, which allows to split the sACHD population into two subgroups: patients at lower risk (CHA_2DS_2-VASc score = 0 or 1 point) and higher risk (CHA_2DS_2-VASc score greater than 1 point).

The current guidelines on the clinical management of adult patients with congenital heart disease consists of heterogeneous and divergent recommendations with a limited level of evidence [18], probably due to the presence/absence of atrial arrhythmias, heterogeneous phenotypes at different levels of cardiovascular risk and poor knowledge of predictors of adverse clinical outcomes [7, 10, 19]. More importantly, the sACHD is traditionally perceived as a curable disease with an excellent prognosis, which does not require long-term follow-up [3, 10, 20] and this vision iterates in cardiological guidelines [1, 19, 20]. However, recent studies have shown different outcomes in terms of life expectancy [5, 8, 9, 20–22] in these patients. Furthermore, although sACHD patients are large and expanding population, in medical literature, they have never been adequately represented [18, 23, 24]. Our results testify that adverse CV events or death are quite frequent in middle-aged people with sACHD (occurring in nearly a quarter of subjects during 6-year follow-up) suggesting a considerable need to search for preventive pharmacological and non-pharmacological strategies based on the knowledge of predisposing factors.

In the present study, we demonstrated that the CHA_2DS_2-VASc score was strongly and independently related to the primary end-point. Our finding is in-line with Yang et al., showing that, for sACHD patients with an average age of 42 years [IQR 32–57], the CHA_2DS_2-VASc risk score ≥ 2 predicted thromboembolic events [18].

In contrast, our results conflict with those published by Khairy et al., which demonstrated that the CHA_2DS_2-VASc risk score was not predictive of thromboembolic events in an unselected population of congenital heart disease patients [25]. These irreconcilable conclusions can be explained by the substantial clinical differences between the population of the two studies: Khairy's patients had AA in the past and in most of them (81%), the complexity of congenital heart disease was moderate-to-severe, while our patients were all sACHDs and predominantly with sinus rhythm. Our sACHD patients were significantly older (mean age at enrollment 53 years vs. 32 years of Khairy's patients), with a higher prevalence of all CV risk factors, chronic ischemic heart disease, HF, and renal failure than those of Khairy. Consequently, these different characteristics led to a relatively higher incidence of thromboembolic in our patients compared to those of Khairy (8% in the 6-year follow-up, respectively, compared to 12% in the 15-year follow-up years). Besides, we considered cardiac events as well as vascular events, making Khairy results more difficult to compare with ours. All these data suggest a better predictive accuracy of the CHA_2DS_2-VASc score in this cohort of patients.

We showed that the dominant prognostic role of the CHA_2DS_2-VASc score in our sACHD patients was unrelated to the presence of AA, being highly accurate in subjects with sinus rhythm. It is a remarkable result that makes applicable the clinical score in all patients with sACHD regardless of the cardiac rhythm and mimics the recent experience on different non-sACHD populations with sinus rhythm and high risk of CV events [12–15]. Finally, almost half of our patients had a prognostic cut-off of CHA_2DS_2-VASc score ≥ 2 corresponding to the value suggested by the international clinical guidelines for prescribing oral anticoagulation in patients with NVAF due to the high risk of adverse outcome [10, 11, 17].

The present study has several limitations that are worthy of note. First, it is a single-center, retrospective study based on routine clinical data integrated with administrative records, so that some sACHD patients could not be recognized for coding errors. Second, there is a lack of information on surgical and post-surgical management, due to the heterogeneous and vast number of congenital heart diseases and the several invasive or conservative strategies adopted in the different cardiac surgery centers, where our patients received their first diagnosis. Third, the data on AA episodes that occurred during follow up are anecdotal and fragmented, so it is not possible to report reliable information on these data, also considering that most of the patients could be asymptomatic or observed in the emergency room without hospitalization. Finally, although the CHA_2DS_2-VASc score was designed to predict the TE, in the sACHD patients, its accuracy as prognosticators of MACE does not seem to derive specifically from stroke, TIA, or TE since cardiac events occur more frequently than TE events. On the other hand, the strengths of the study consist in the complete nature of the data set, the duration of the follow up, the high event rate, the large sample size, and the accessibility to all prognostic information.

Our findings show that in middle-aged sACHD patients, the rate of CV events or death is quite high in the long term, and that the CHA_2DS_2-VASc score is an accurate predictor of adverse outcomes regardless of the cardiac rhythm. Almost half of these patients have CHA_2DS_2-VASc score higher than 1 point, representing a status at higher risk. Further evaluations and surveys should be undertaken to assess the clinical conditions and the need for specific treatments mainly aimed at optimizing the control of CV risk factors.

Author Contribution GF contributed to the conception, design of the work and writing the manuscript. GC contributed to the data analysis and critical review of the manuscript. GB and AS contributed to the data analysis and the drafting of the manuscript. GR, CM, MZ and BAM contributed to the data acquisition. ADL and GS contributed to the data interpretation and critical review of the manuscript. All authors

gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies involving human and animal participants performed by any of the authors.

Informed Consent Informed consent, either from patients or parents, was legibly obtained according to the institution policy in whom interventional procedures were performed and who were included in the study.

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