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The predictive value of the CHA2DS2-VASc score in patients with mechanical mitral valve thrombosis

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Abstract

Prosthetic valve thrombosis (PVT) is a potentially life-threatening complication associated with high morbidity and mortality. The CHA2DS2-VASc is a clinical score used to determine thromboembolism risk in non-valvular atrial fibrillation patients. Therefore; in this study, we aimed to determine predictive value of the CHA2DS2-VASc score for development of PVT in patients with mechanical prosthetic valve. This was a retrospective study included 417 consecutive patients with mechanic prosthetic valve in whom transesophageal echocardiography (TEE) was performed due to different clinical indications from January 2004 to June 2016. After evaluation according to exclusion criteria, 267 patients with mechanic prosthetic valve were enrolled in the study. The definitive diagnosis of the PVT was made as proposed by TEE finding. The study population was divided into two groups; PVT patients (154 patients) and control group (113 patients) with functional prosthetic valve. The CHA2DS2-VASc score was calculated for each patient from the hospital electronic database. The mechanical mitral valve thrombosis predictive value of variables including CHA2DS2-VASc score was tested in our study. The mean CHA2DS2-VASc score was significantly higher in PVT patients compared to control patients (2.51 ± 1.54 vs. 1.13 ± 1.21, $p < 0.01$). Both on univariate and multivariate analysis demonstrated that the CHA2DS2-VASc score is independently associated with PVT ($p < 0.001$ and $p < 0.001$, respectively). The patients whose CHA2DS2-VASc score ≥ 1–3 had 6.20 times higher risk for thrombus formation, and patients whose CHA2DS2-VASc score ≥ 4 had 16.6 times higher risk for thrombus formation compared to patients with CHA2DS2-VASc score $= 0$ ($p < 0.001$ and $p < 0.001$, respectively). The CHA2DS2-VASc score may be a significant independent predictor of PVT in patients with prosthetic valve and the CHA2DS2-VASc score ≥ 2.5 or more was associated with increased PVT in patients with prosthetic valve. Thus; it may be an applicable risk scoring system to assess the risk of development of PVT in patients with prosthetic valve.

Keywords Prosthetic valve thrombosis · CHA2DS2-VASc score · Mitral valve

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Introduction

Prosthetic valve thrombosis (PVT) is a rare but well-known and life-threatening complication of surgical valve replacement associated with significant morbidity and mortality. The incidence of PVT is 0.03% in bioprosthetic valves and has varied from roughly 0.5% to as high as 8% in mechanic prosthetic valves in the mitral and aortic positions [1, 2]. Incomplete prosthesis, leaflet damage, leaflet deterioration and prosthesis malpositioning, low cardiac output, and ineffective anticoagulation are the demonstrated risk factors in the development of prosthetic valve thrombus formation [3]. It has been demonstrated that approximately 10% of the patients with mechanical heart valves had one episode of PVT per year [4].

The CHA2DS2-VASc risk score is an inexpensive, simple and easy scoring system which is calculated by assigning 1 point for each; congestive heart failure (ejection fraction < 40%), hypertension, age between 65 and 74 years, diabetes mellitus, vascular disease (myocardial infarction or peripheral arterial disease) and female sex, 2 points for; a history of stroke or transient ischemic attack (TIA) and age > 75 years [5]. The CHA2DS2-VASc risk score estimates the thromboembolism risk in non-valvular atrial fibrillation (NVAF) patients. Previous studies investigated the clinical application and importance of this score in acute coronary syndromes [6]. Also, it had been showed that there is corroboration between this scoring system and left atrial thrombus [7, 8]. From this point of view, in this study, we aimed to determine the predictive value of the CHA2DS2-VASc score with the presence of thrombus in prosthetic valve patients.

Patients and methods

Patient population

A total of 417 consecutive transesophageal echocardiography (TEE) examinations performed in patients with mechanical prosthetic valve in the mitral position due to different clinical indications at our institution between January 2004 to June 2016 were respectively reviewed. The patients with fever or signs of infection (28 patients, 6.7%) (Suspected infective endocarditis), who had prosthetic valve obstruction without a thrombus (25 patients, 6.0%), and with moderate to severe para-valvular regurgitation without thrombus (97 patients, 23.2%) were excluded from the study. Since the thrombosis of bioprosthetic valve is a rare clinic entity when compared to mechanical prostheses, patients with bioprosthetic valve thrombosis were not included in the study. After evaluation according to exclusion criteria, 267 patients with prosthetic valve in the mitral position were enrolled in the study. The 154 patients diagnosed with PVT upon TEE examination and 113 patients with functional prosthetic valve as the controls composed of the study population (Fig. 1). The CHA2DS2-VASc score of each patient was calculated using clinical data obtained from the hospital electronic database. Two points were assigned for age > 75 years and a history of stroke or transient ischemic attack (TIA) and, 1 point was assigned for hypertension, age between 65 and 74 years, diabetes mellitus, heart failure, female sex and vascular disease (myocardial infarction or peripheral arterial disease) (PAH). Transthoracic echocardiogram (TTE) is usually the initial diagnostic tool for diagnosis of PVT but TEE is the gold standard diagnostic tool because of providing a better assessment of the prosthetic valve. Therefore, we used TEE for the definitive diagnosis of PVT in the study. The study was approved by the local ethic board.

Transesophageal echocardiography examination

After overnight fasting, TEE examinations were performed in a standard manner, with all subjects in the lateral

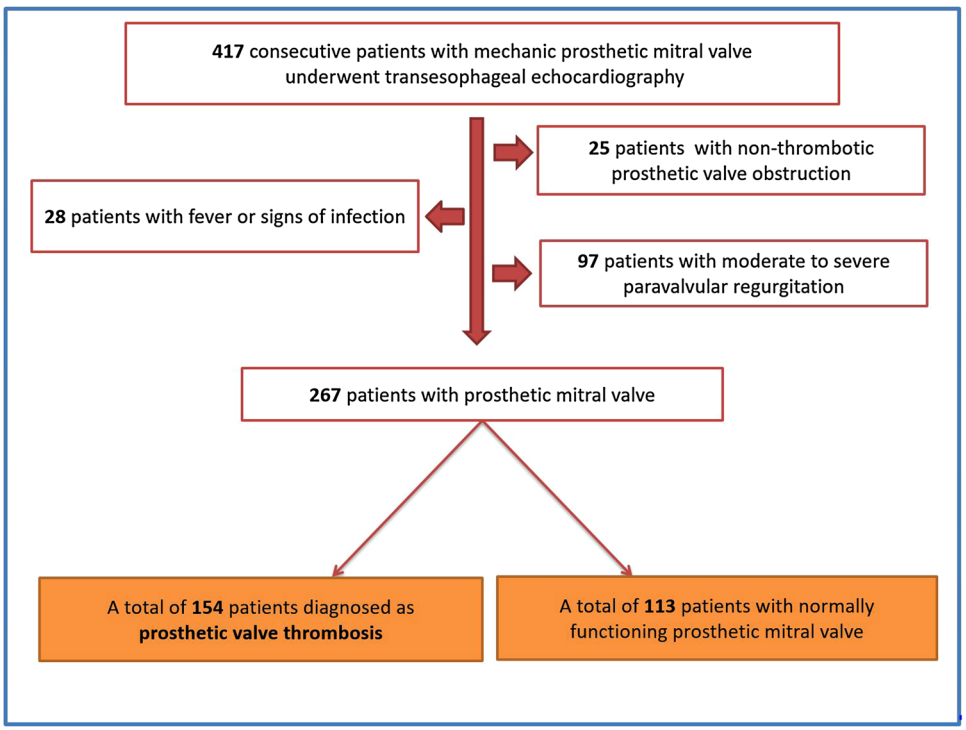

Fig. 1 The flow chart of the study population

decubitus position, using the Vivid-Med System Seven with a multiplane TEE probe (GE Medical Systems, Hortan, Norway). Informed consent was obtained just to perform the TEE procedure. TEE was performed under conscious sedation with anaesthetizing the hypopharynx. Multiple views were acquired and analyzed by two blindly cardiologists (M.I.H and A.O.). Thrombus was identified as a homogeneous, more mobile, or fixed mass with lower in density than pannus located at the valve occluder or valve struts and was visualized in all patients with PVT [9]. As previously shown, the differentiation of thrombus from pannus over-growth was relied on TEE findings [9–11].

Laboratory data analysis

Venous blood samples were obtained from all patients for hematological and biochemical measurements before the TEE examination. An automated complete counting a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland) were used to measure hematologic parameters.

Definitions

Hypertension was described as undergoing anti-hypertensive treatment or a systolic pressure > 140 mmHg, and/or a diastolic pressure > 90 mmHg on at least two separate measurements during hospitalization [12]. Diabetes mellitus was described as taking oral antidiabetics or insulin, or follow up fasting blood glucose levels fulfilling the American Diabetes Association's criteria [13]. Stroke was defined as a neurologic deficit lasting < 24 h as TIA or if longer as stroke. Preexisting chronic renal failure was defined as having an eGFR < 60 mL/min/1.73 m^2 for > 3 months with or without kidney damage [14]. Ineffective coagulation was described as one or more measurement of international normalized ratio with value of below 2 within the last 3 months.

Statistical analysis

Data was analyzed with Statistical Package for Social Sciences (SPSS) version 20.0 for Windows (IBM, Armonk, New York). Normality of distribution was assessed using Kolmogorov–Smirnov test. Normally distributed scale variables were expressed as mean ± standard deviation. Categorical variables were presented as number and percentages. Differences in the median values between groups were analyzed using Mann–Whitney U test. Categorical variables were analyzed by Chi square test or Fisher's exact test. Multivariate analysis by stepwise logistic regression models (backward elimination) tested variables that were significant at $p < 0.25$ in the univariate analysis. Statistical significance was defined as a p value < 0.05.

Results

The total study population was consisted of total 267 patients with mechanical prosthetic valve in the mitral position. The study population was divided into two groups; PVT patients (154 patients) and control group (113 patients) with functional prosthetic valve. The 138 patients with PVT had mechanic prosthetic valve type as a bi-leaflet (89.6%) and 16 patients had a single tilting disc type mechanic valve (10.4%). On the other hand, in the control group, bi-leaflet mechanic valve type patients were 98 patients (86.7%); the others were mechanic prosthetic single tilting disc type valve (15 patients, 13.3%). Mechanic prosthetic valve type as single tilting disc or bi-leaflet was similar between the two groups ($p > 0.05$). Baseline characteristics, echocardiographic and laboratory findings were listed in Table 1. The patients in PVT group were older, female, hypertensive, diabetic, had more congestive heart failure (CHF) and cerebrovascular accident (CVA) compared with control group. ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.034$, $p < 0.001$ and $p < 0.001$ respectively). The two groups were similar in terms of chronic renal failure (CRF), peripheral artery disease (PAH),chronic obstructive pulmonary disease (COPD), coronary artery disease, myocardial infarction and AF ($p > 0.05$).Whereas, ineffective coagulation was significantly higher in PVT group ($p < 0.001$). Besides that, the two groups were similar in terms of laboratory and echocardiographic findings ($p > 0.05$).

The mean CHA2DS2-VASc score was significantly higher in PVT patients compared to control patients (2.51 ± 1.54 vs. 1.13 ± 1.21, $p < 0.001$). The frequency of patients whose CHA2DS2-VASc score = 0 (38.9% vs. 3.2%, $p < 0.001$) was higher and the frequency of patients whose CHA2DS2-VASc score ≥ 1–3 (56.6% vs. 78.6%, $p < 0.001$) and CHA2DS2-VASc score ≥ 4 were lower in the control group (4.4% vs. 18.2%, $p = 0.001$) compared to PVT group.

Results of univariate and multivariate analysis were shown in Table 2. In univariate regression analysis, ejection fraction, blood urea nitrogen, ineffective anticoagulation and the CHA2DS2-VASc score were found to be predictors of mechanical mitral valve thrombosis in the study population. In multivariate regression analysis, using model adjusted for the aforementioned parameters, the CHA2DS2-VASc score (Odds ratio [OR] 1.39, 95% confidence interval [CI] 1.02–1.90, $p = 0.036$) and ineffective anticoagulation (OR 3.88, 95% CI 1.70–8.86, $P = 0.001$) were found to be independent predictors of mechanical mitral valve thrombosis. The patients whose CHA2DS2-VASc score ≥ 1–3 had 6.20 times higher risk for thrombus formation, and patients whose CHA2DS2-VASc score

Table 1 Baseline characteristics, echocardiographic and laboratory findings of prosthetic valve thrombosis patients and control group

	Control, n = 113	Prosthetic valve thrombosis, n = 154	p value
Age (years)	51 ± 12	57 ± 11	< 0.001
Male gender	65 (57.5%)	47 (30.5%)	< 0.001
Hypertension	25 (22.1%)	68 (44.2%)	< 0.001
Diabetes mellitus	10 (8.8%)	28 (18.2%)	0.031
Chronic renal failure	5 (4.4%)	16 (10.4%)	0.074
Peripheral artery disease	3 (2.7%)	7 (4.5%)	0.526
Chronic obstructive pulmonary disease	10 (8.8%)	25 (16.2%)	0.077
Coronary artery disease	15 (13.3%)	29 (18.8%)	0.227
Myocardial infarction	7 (6.2%)	10 (6.5%)	0.921
Congestive heart failure	5 (4.4%)	43 (27.9%)	< 0.001
Cerebrovascular accident	2 (1.8%)	26 (16.9%)	< 0.001
Atrial fibrillation	67 (59.3%)	97 (63.0%)	0.540
Ineffective anticoagulation	23 (20.4%)	106 (68.8%)	< 0.001
Ejection fraction (%)	52 ± 7	48 ± 11	0.071
Left atrium anteroposterior (mm)	49 ± 8	50 ± 7	0.325
Postoperative period (months)	57.8 ± 27.2	59.4 ± 29.7	0.802
Mechanic valve type			
Single tilting disc	15 (13.3%)	16 (10.4%)	0.467
Bi-leaflet	98 (86.7%)	138 (89.6%)	0.467
CHA_2DS_2-VASc score	1.13 ± 1.21	2.51 ± 1.54	< 0.001
CHA_2DS_2-VASc = 0	44 (38.9%)	5 (3.2%)	< 0.001
CHA_2DS_2-VASc = 1–3	64 (56.6%)	121 (78.6%)	< 0.001
CHA_2DS_2-VASc ≥ 4	5 (4.4%)	28 (18.2%)	0.001
Laboratory variables			
White blood cell (cells/μL)	7.85 ± 2.50	7.58 ± 3.20	0.065
Hemoglobin (g/dL)	12.1 ± 2.1	12.2 ± 1.7	0.927
Hematocrit (%)	35.9 ± 5.8	36.2 ± 4.9	0.628
Platelets (/mm^3)	249.9 ± 94.7	234.4 ± 93.2	0.173
Lymphocytes (cells/μL)	1.87 ± 0.73	1.84 ± 0.70	0.703
MCV	84.7 ± 7.8	84.9 ± 6.9	0.684
RDW	15.7 ± 2.8	15.8 ± 2.3	0.508
MPV	8.9 ± 1.1	9.0 ± 1.1	0.363
Creatinine (mg/dL)	0.90 ± 0.58	0.99 ± 0.53	0.099
BUN	17.7 ± 8.7	20.8 ± 13.0	0.054

Continuous variables are presented as mean ± SD. Nominal variables presented as frequency (%)

MCV mean cell volume, *RDW* red cell distribution width, *MPV* mean platelet volume, *BUN* blood urea nitrogen, *EF* ejection fraction, *LA* left atrium

≥ 4 had 16.6 times higher risk for thrombus formation compared to patients with CHA2DS2-VASc score = 0 ($p < 0.001$ and $p < 0.001$). An receiver operating characteristic (ROC) analysis was used to show the best cut-off value of the CHA2DS2-VASc score to predict PVT was ≥ 2.5 with 54% sensitivity and 87% specificity [area under curve (AUC): 0.76; 95% CI 0.70–0.82; $p < 0.001$] (Fig. 2). A box plot was drawn to show the difference between the CHA2DS2-VASc values of PVT and control groups (Fig. 3).

Discussion

In this study, we have shown that the CHA2DS2-VASc score has a strong and independent predictive value for the occurrence of PVT in surgically implanted left sided mechanical prosthetic valve patients and every one point increase in the CHA2DS2-VASc score increases the risk of PVT. Patients especially whose CHA2DS2-VASc score ≥ 4 had 16.6 times higher risk for development of PVT

Table 2 Univariate predictors and multivariate model for prosthetic valve thrombosis

Univariate analysis	P value	Multivariate analysis	P value	OR (95% CI)
Age[a]	< 0.001			
Hypertension[a]	< 0.001			
Diabetes mellitus[a]	0.034			
Gender[a]	< 0.001			
Congestive heart failure[a]	< 0.001			
Cerebrovascular accident[a]	0.001			
Chronic obstructive pulmonary disease	0.082			
Chronic renal disease	0.082			
Ejection fraction	0.003			
Platelets	0.205			
Blood urea nitrogen	0.045			
Postoperative period (months)	0.651			
Ineffective anticoagulation	< 0.001	Ineffective anticoagulation	0.001	3.88 (1.70–8.86)
CHA_2DS_2-VASc score	< 0.001	CHA_2DS_2-VASc score	0.036	1.39 (1.02–1.90)
CHA2DS2-VASc = 0				Reference
CHA2DS2-VASc = 1–3	< 0.001		< 0.001	6.20 (2.10–19.42)
CHA2DS2-VASc ≥ 4	< 0.001		< 0.001	16.6 (6.28–44.03)

All clinically relevant parameters were included in the model. Only parameters that reached statistical significance at univariate analysis were given in the left most columns

OR odds ratio, *CI* confidence interval

[a]These parameters were not included in the multivariable model as they are components of the CHA2DS2-VASc score

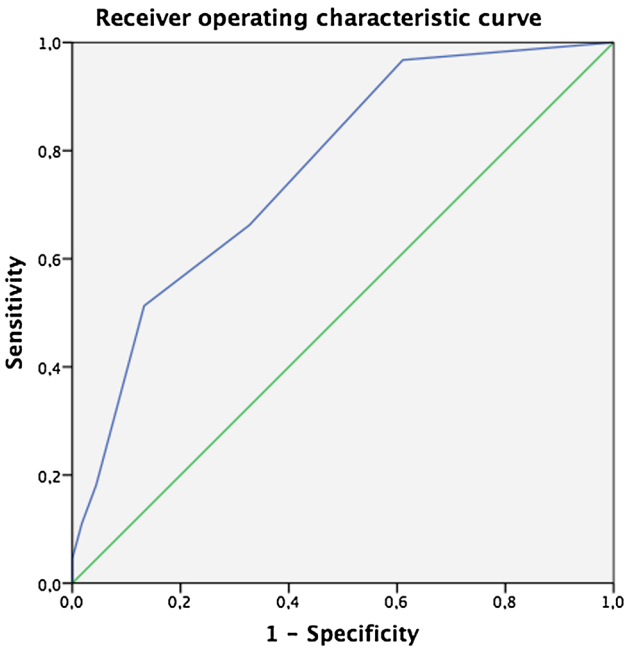

Fig. 2 The ROC curve of the CHA2DS2-VASc score. The CHA2DS2-VASc score had an area under the curve value of 0.76 (95%CI 0.70–0.82, p < 0.001) on the ROC curve. The best cut-off value of the CHA_2DS_2-VASc score to predict the PVT was ≥ 2.5 with 54% sensitivity and 87% specificity

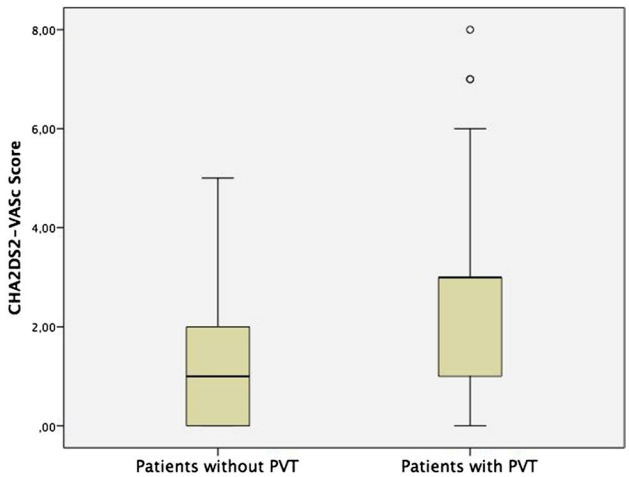

Fig. 3 The box plot illustrating the difference between the CHA2DS2-VASc values of PVT and control groups. *ROC* receiver operating characteristic curve, *PVT* prosthetic valve thrombosis

compared to patients with whom CHA2DS2-VASc score = 0.

Recent developments in valve structure and surgical techniques have produced better prognosis in patients with mechanical prosthetic valve. However, the thrombotic feature of mechanical prosthetic valve remains the main source of complications [15]. PVT is a rare but dreadful

complication of the prosthetic valves. Surface, hemodynamic and hemostasis related factors are the main mechanisms for the development of PVT [16]. For hemodynamic factors, particularly low flow or reduced cardiac output, can favor thrombosis, hence, more patients with PVT compared to control group had lower ejection fraction and CHF in the study [17]. Hypercoagulability is a less frequent mechanism in PVT, but may be an important contributor in high-risk patients. Franchini et al. demonstrated that plasma concentration of certain coagulation factors (factor V, VII, VIII, IX, fibrinogen) increase progressively with age [18]. Also, female gender, hypertension and diabetes mellitus are shown that associated with hypercoagulability state in the body [19–21]. It was shown in previous studies that ineffective anticoagulation is the main risk factor for development of PVT [17] and, in agreement with others; the present study revealed that ineffective anticoagulation was common in patients with PVT and causes a great tendency for the development of PVT. Owing to thrombosis of bioprosthetic valve is a rare clinic entity when compared to mechanical prostheses, all the patients included in our data had thrombosis on mechanical prosthetic valve [17]. Durrleman et al. reported the cohort of 39 patients presented with PVT [22]. In this series; most patients with PVT were female, older, hypertensive and in most of the case underlying pathology involved the mechanic mitral prostheses as similar to our study.

The CHA2DS2-VASc score has been mainly developed for the assessment of thromboembolic risk in patients with NVAF. Chua et al. and Podolecki et al. demonstrated an association between the CHA2DS2-VASc score and a significant increase in adverse cardiovascular outcomes in patients with acute coronary syndrome (ACS) regardless of the presence of AF [23, 24]. In addition, a growing body of evidence showed an association between the CHA2DS2-VASc score and left atrium thrombus [25]. Nevertheless, there are no data regarding occurrence of PVT in patient with prosthetic valve according to their CHA2DS2-VASc score. The current study was designed to evaluate the predictive value of the CHA2DS2-VASc score in patients with PVT and was able to show an every point increase in score increases the risk of PVT.

CHF, older age, female gender, hypertension and diabetes mellitus were found as risk factors for the development of PVT on univariate analysis in the study most probably because of providing hypercoagulability circumstance in the body as previously mentioned. Besides that, these factors are also used in calculations of the CHA2DS2-VASc risk score. Therefore, these common risk factors may help us to explain why the CHA2DS2-VASc score may predict PVT. The current guidelines recommend the use of imaging modalities only in the presence of potential valve-related symptoms or starting 10 years after the valve implantation [16]. However, PVT in patients with prosthetic valve may range from an incidental finding at the time of echocardiographic follow-up to cardiogenic shock [16]. Also, mortality in patients with PVT remains high and there is no guideline based clinical score for predicting PVT. The CHA2DS2-VASc risk score is easy to apply and familiar to clinicians in daily practice. Thus, we suppose that the CHA2DS2-VASc risk score may especially have clinical use in patients with high-risk score. Mechanic prosthetic valve that have a low risk of thrombogenicity profile or bioprosthetic valve may be preferred in patients whose CHA2DS2-VASc risk score is high before the surgical operation. In addition, the patients who had a mechanic prosthetic valve may be closely monitored with frequent international normalized ratio (INR). According to the current guidelines, once the patient has had two consecutive INRs in the target range, warfarin recipients may undergo INR testing every 4 weeks. However, patients with high CHA2DS2-VASc score may need more frequent INR testing such as 2–3 weeks interval or frequent monitoring may need to be increased as a patient's CHA2DS2-VASc score increases over time or in case of any drug that intervenes the warfarin due to high risk of development of PVT. Besides that, the AF that could be involved in the thrombotic process of valve prosthesis did not differ between the groups implies that the CHA2DS2-VASc score may have a predictive value in patients with prosthetic valve for the development of PVT regardless of AF.

Study limitations

It was a single center, retrospective and observational study with limited number of patients and has inherent limitations of a retrospective design. Also, there might be selection bias, but, we were careful to include consecutive patients. Besides that, histo-pathological confirmation that is compulsory for the definitive diagnosis of PVT has not been provided from the patients. However, TEE which is the gold standard diagnostic tool for diagnosis of PVT was used in the study. Moreover, the patient who had prosthetic valve obstruction without a thrombus was excluded from the study to increase the reliability of the findings. Since the patients with PVT in the mitral position were included in the study, we could not evaluate the predictive value of the CHA2DS2-VASc score in patients with PVT in the aortic position.

Conclusion

This is the first study that showed a predictive value of the CHA2DS2-VASc score for development of PVT in patients with mechanical prosthetic valve. In particularly, the patients whose CHA2DS2-VASc score was ≥ 4 have 16.6 times higher risk for development of PVT. Hence; it may be an applicable risk scoring system to assess the risk

of development of PVT in patients with prosthetic valve. However, since it was retrospective study, multicenter and prospective studies are necessary for validation of this scoring system.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Research involving human and animal participants This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained just to perform the TEE procedure.

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