Original Article

Value of Combining Left Atrial Diameter and Amino-terminal Pro-brain Natriuretic Peptide to the CHA2DS2-VASc Score for Predicting Stroke and Death in Patients with Sick Sinus Syndrome after Pacemaker Implantation

Bin-Feng Mo, Qiu-Fen Lu, Shang-Biao Lu, Yu-Quan Xie, Xiang-Fei Feng, Yi-Gang Li

Department of Cardiology, Xinhua Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai 200092, China

Abstract

Background: The CHA2DS2-VASc score is used clinically for stroke risk stratification in patients with atrial fibrillation (AF). We sought to investigate whether the CHA2DS2-VASc score predicts stroke and death in Chinese patients with sick sinus syndrome (SSS) after pacemaker implantation and to evaluate whether the predictive power of the CHA2DS2-VASc score could be improved by combining it with left atrial diameter (LAD) and amino-terminal pro-brain natriuretic peptide (NT-proBNP).

Methods: A total of 481 consecutive patients with SSS who underwent pacemaker implantation from January 2004 to December 2014 in our department were included. The CHA2DS2-VASc scores were retrospectively calculated according to the hospital medical records before pacemaker implantation. The outcome data (stroke and death) were collected by pacemaker follow-up visits and telephonic follow-up until December 31, 2015.

Results: During 2151 person-years of follow-up, 46 patients (9.6%) suffered stroke and 52 (10.8%) died. The CHA2DS2-VASc score showed a significant association with the development of stroke (hazard ratio [*HR*] 1.45, 95% confidence interval [*CI*] 1.20–1.75, $P < 0.001$) and death (*HR* 1.45, 95% *CI* 1.22–1.71, $P < 0.001$). The combination of increased LAD and the CHA2DS2-VASc score improved the predictive power for stroke (C-stat 0.69, 95% *CI* 0.61–0.77 vs. C-stat 0.66, 95% *CI* 0.57–0.74, $P = 0.013$), and the combination of increased NT-proBNP and the CHA2DS2-VASc score improved the predictive power for death (C-stat 0.70, 95% *CI* 0.64–0.77 vs. C-stat 0.67, 95% *CI* 0.60–-0.75, $P = 0.023$).

Conclusions: CHA2DS2-VASc score is valuable for predicting stroke and death risk in patients with SSS after pacemaker implantation. The addition of LAD and NT-proBNP to the CHA2DS2-VASc score improved its predictive power for stroke and death, respectively, in this patient cohort. Future prospective studies are warranted to validate the benefit of adding LAD and NT-proBNP to the CHA2DS2-VASc score for predicting stroke and death risk in non-AF populations.

Key words: Amino-terminal Pro-brain Natriuretic Peptide; CHA2DS2-VASc Score; Left Atrial Diameter; Risk Stratification; Sick Sinus Syndrome

Introduction

Stroke is a disease with high mortality and morbidity, and approximately 15% of all strokes are attributed to nonvalvular atrial fibrillation (AF).[1] Many risk stratification schemes have been developed to help evaluate the risk of stroke in patients with AF, with the CHA2DS2-VASc score being the most commonly used tool.[2,3]

Recently, the use of the CHA2DS2-VASc score in predicting stroke and death has extended beyond AF patients[4-7] and was reported to show a significant association with stroke and death in patients with sick sinus syndrome (SSS) and implanted pacemakers from the DANPACE study.[8]

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.211881

Address for correspondence: Dr. Yi-Gang Li, Department of Cardiology, Xinhua Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai 200092, China
E-Mail: liyigang@xinhuamed.com.cn

Received: 16-03-2017 **Edited by:** Yuan-Yuan Ji

How to cite this article: Mo BF, Lu QF, Lu SB, Xie YQ, Feng XF, Li YG. Value of Combining Left Atrial Diameter and Amino-terminal Pro-brain Natriuretic Peptide to the CHA2DS2-VASc Score for Predicting Stroke and Death in Patients with Sick Sinus Syndrome after Pacemaker Implantation. Chin Med J 2017;130:1902-8.

However, there are limited data about the risk score for predicting stroke and death in Chinese patients with SSS with implanted pacemakers.

It is known that the discriminatory capability of the CHA2DS2-VASc score in risk stratification is modest in the AF population,[9] and efforts have been made to improve the discrimination capability of CHA2DS2-VASc score by collectively evaluating echocardiographic parameters and biomarkers in patients with AF.[10]

Left atrial diameter (LAD) measured by transthoracic echocardiography and serum amino-terminal pro-brain natriuretic peptide (NT-proBNP) are two of the simplest variables commonly used in daily clinical practice for the assessment of cardiac remodeling and disease progression status. LAD was found to be an independent predictor of stroke,[11] and the related left atrial volume could significantly improve the predictive power of the CHA2DS2-VASc score for the presence of left atrial thrombus or dense spontaneous echo contrast[12] in patients with nonvalvular AF. A recent study has demonstrated that NT-proBNP provided complementary prognostic information to the CHA2DS2-VASc score for the prediction of stroke and death in anticoagulated patients with AF.[13]

In the present study, we tested the hypotheses that the CHA2DS2-VASc score could predict stroke and death in Chinese patients with SSS after pacemaker implantation and that adding LAD and NT-proBNP to CHA2DS2-VASc score could improve its predictive power for stroke and death in this patient cohort.

Methods

Ethical approval

Given the retrospective study design and the fact that data analysis was performed anonymously, this study was approved by the Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University, School of Medicine, and was exempt from obtaining informed consent from patients.

Subjects

Consecutive SSS patients who underwent pacemaker implantation in our department from January 2004 to December 2014 were included. SSS was defined as symptomatic bradycardia; documented sinoatrial block or sinus-arrest with pauses >3 s or sinus bradycardia <40 beats/min for >1 min while awake; and QRS width <0.12 s. Exclusion criteria were defined as one or more of the following: II or III degree atrioventricular block, bifascicular block or trifascicular block, persist or permanent AF, rheumatoid valvular heart disease, or a history of ventricular tachycardia.

A history of paroxysmal AF (pAF) was not an exclusion criterion. Patients with pAF at baseline were identified by electrocardiogram (ECG) or Holter. Clinical data, including information relating to previous medical history, laboratory test/imaging, and medication, were collected from hospital medical records. Congestive heart failure (HF) was considered present for patients with a history of HF or New York Heart Association III–IV level or a measured left ventricular ejection fraction ≤0.40. The CHA2DS2-VASc scores (congestive HF, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65–74 years, sex category [female]) were retrospectively calculated from data collected at admission before pacemaker implantation.

Left atrial diameter and amino-terminal pro-brain natriuretic peptide

Transthoracic echocardiography and blood tests were done before the pacemaker implantation. LAD was measured using M-mode or two-dimensional echocardiography, from the posterior aortic wall to the posterior left atrial wall, in the parasternal long axis view at the end-ventricular systole. Concentrations of plasma NT-proBNP were measured by an electrochemiluminescence immunoassay. A value of LAD ≥35 mm for women or ≥40 mm for men was assigned one point, and a value of NT-proBNP ≥400 pg/ml was also assigned one point. These were added to the original CHA2DS2-VASc score.

Pacemaker implantation

We implanted the pacemaker electrodes via the cephalic vein or subclavian vein. The ventricular electrodes were implanted in the right ventricular septa or right ventricular apex and the atrial electrodes were implanted in the right auricle for dual-chamber pacemakers (DDD). The ventricular electrodes were implanted in the right ventricular septa or right ventricular apex for single-chamber pacemakers (VVI).

Follow-up and outcomes

Pacemaker follow-up visits were made at 1, 3, and 6 months and then once half a year after pacemaker implantation. Pacemaker testing was made at each clinical visit, and patients were also evaluated for cardiovascular events (myocardial infarction, stroke, and syncope).

The primary endpoint was the hospital diagnosis of stroke after pacemaker implantation. Stroke was defined as the sudden development of focal neurological symptoms lasting >24 h due to vascular factors. Stroke events were diagnosed by neurologists or emergency medicine specialists and were confirmed by computed tomography in 90.4% of cases. The secondary endpoint was all-cause death. The outcome (stroke and death events) data of patients were collected at the pacemaker follow-up visits and via telephonic follow-up until December 31, 2015.

Statistical analysis

Baseline characteristics were described using percentages for categorical variables and medians (interquartile range) for age. Characteristics were compared across score subgroups using the Wilcoxon rank-sum test for age and the Chi-square test for categorical variables. For the purposes

of summarizing event rates, we arbitrarily divided the CHA2DS2-VASc score into three categories: low (0–1), medium (2–4), and high (5–9). Event rates were summarized as events per 100 patient-years among the subgroups. Cox regression was performed to assess the ability of the CHA2DS2-VASc score to independently predict stroke and death. We calculated the C-statistics for both endpoints to evaluate the discriminatory power of the CHA2DS2-VASc score, as well as the addition of LAD, NT-proBNP, or both to the score. C-statistics were compared using the DeLong test. Statistical tests were two-tailed, and $\alpha = 0.05$ was the significance level in this study. All analyses were performed using SAS 8.02 (SAS Institute, Cary, NC, USA) and MedCalc 15.2 (Microsoft Corporation, Redmond, WA, USA).

Results

The study population comprised 481 consecutive patients with SSS and implanted pacemakers, 34.7% with a diagnosis of proximal AF at baseline. The median follow-up time was 40 (28, 67) months. The median age was 75 (69, 81) years and women comprised 59.3% of the study population. Totally, 378 cases (78.6%) were implanted with a DDD pacemaker, while 103 cases (21.4%) were implanted with a VVI pacemaker. The distribution of patients with SSS in the CHA2DS2-VASc categories is shown in Table 1. Baseline characteristics of patients stratified according to the CHA2DS2-VASc score are shown in Table 2. The baseline cardiovascular risk factors significantly increased as the CHA2DS2-VASc score increased.

During 2151 patient-years of follow-up, a total of 52 strokes were reported in 46 patients, and these 46 patients were analyzed as the primary endpoints in this study. Forty-seven strokes were identified by physicians and confirmed by imaging, while five strokes were clinically diagnosed by physicians. Among those confirmed by imaging, 44 were ischemic stroke and three were hemorrhagic stroke. Twenty-four (7.6%) patients without baseline pAF and 22 (13.2%) patients with baseline pAF had a subsequent diagnosis of stroke ($P = 0.050$). A total of 52 deaths were reported in this study, 28.8% of which were cardiac death. Twenty-five (8.0%) patients without baseline pAF and 27 (16.2%) patients with baseline pAF died ($P = 0.006$).

The average incidence of stroke was 2.1 events per 100 patient-years and the average incidence of death was 2.4 events per 100 patient-years in these patients with SSS. The incidence of stroke and death increased along with the CHA2DS2-VASc score, exhibiting a clear "dose–response" relationship [Figure 1]. Indeed, the incidence of stroke was above four events per 100 patient-years in patients with CHA2DS2-VASc scores ≥5.

Data from the univariate analysis showed that increased NT-proBNP was statistically associated with stroke and death, while increased LAD was only significantly associated with stroke. However, after adjusting for clinical risk factors (age, sex, AF history, type of pacemakers, oral anticoagulation, and aspirin administration; the presence of congestive HF, hypertension, diabetes, previous stroke/TIA/TE, and vascular disease), increased LAD alone remained an independent risk factor for the outcome of stroke (hazard ratio [*HR*] 4.20, 95% confidence interval [*CI*] 1.83–9.62, $P < 0.001$) [Table 3].

The CHA2DS2-VASc score showed a significant association with the development of stroke (*HR* 1.45, 95% *CI* 1.20–1.75, $P < 0.001$) and death (*HR* 1.45, 95% *CI* 1.22–1.71, $P < 0.001$). The new scores, formed by the addition of increased LAD, increased NT-proBNP, or both to the CHA2DS2-VASc score, were also significantly associated with the risk of stroke and death [Table 4].

The C-statistics of adding increased LAD, increased NT-proBNP, or both to the CHA2DS2-VASc score were evaluated by receiver operating characteristic analysis. The combination of increased LAD and the CHA2DS2-VASc score showed improved predictive power for stroke (C-stat 0.69, 95% *CI* 0.61–0.77 vs. C-stat

Table 1: Distribution of the CHA2DS2-VASc score in all SSS patients

CHA2DS2-VASc score	SSS patients (*n* = 481)	AF-free patients (*n* = 314)	AF patients (*n* = 167)
0–1	67 (13.9)		
0	18 (3.7)	15 (4.8)	3 (1.8)
1	49 (10.2)	38 (12.1)	11 (6.6)
2–4	298 (62.0)		
2	68 (14.1)	47 (15.0)	21 (12.6)
3	112 (23.3)	76 (24.2)	36 (21.6)
4	118 (24.5)	71 (22.6)	47 (28.1)
5–9	116 (24.1)		
5	69 (14.4)	41 (13.1)	28 (16.8)
6	29 (6.0)	15 (4.8)	14 (8.4)
7	13 (2.7)	7 (2.2)	6 (3.6)
8	2 (0.4)	1 (0.3)	1 (0.6)
9	3 (0.6)	3 (1.0)	0

Values are present by *n* (%). SSS: Sick sinus syndrome; AF: Atrial fibrillation.

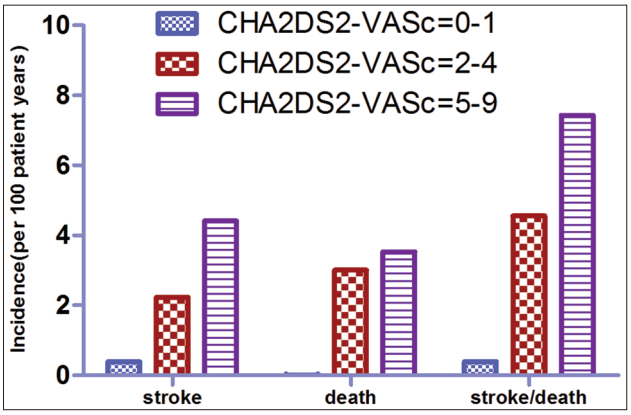

Figure 1: Risks of ischemia stroke and death according to the CHA2DS2-VASc score.

Table 2: Baseline characteristics of SSS patients with implanted pacemakers stratified according to the CHA2DS2-VASc score

Characteristics	CHA2DS2-VASc score			Statistics	*P*
	0–1	2–4	5–9		
Number of patients, *n* (%)	67 (13.9)	298 (62.0)	116 (24.1)	–	–
Age (years), median (Q_1, Q_3)	60 (55, 65)	75 (70, 80)	80 (77, 83)	166.126‡	<0.001
Female, *n* (%)	22 (32.8)	179 (60.1)	84 (72.4)	27.769§	<0.001
Dual-chamber pacemaker, *n* (%)	60 (89.6)	228 (76.5)	90 (77.6)	5.620§	0.060
Medical history, *n* (%)					
Paroxysmal AF	14 (20.9)	104 (34.9)	49 (42.2)	8.549§	0.014
Congestive heart failure	0	26 (8.7)	59 (50.9)	118.611§	<0.001
Hypertension	12 (17.9)	208 (69.8)	108 (93.1)	111.637§	<0.001
Age ≥75 years	0	160 (53.7)	104 (89.7)	138.318§	<0.001
Diabetes	1 (1.5)	24 (8.1)	45 (38.8)	74.126§	<0.001
Previous stroke/TIA/TE	0	10 (3.4)	35 (30.2)	78.841§	<0.001
Vascular disease	0	62 (20.8)	70 (60.3)	95.000§	<0.001
Previous MI	0	9 (3.0)	7 (6.0)	5.037§	0.081
Chronic renal disease	1 (1.5)	11 (3.7)	15 (13.0)	16.884§	<0.001
Increased LAD*, *n* (%)	11 (16.4)	144 (48.3)	70 (60.3)	33.667§	<0.001
Increased NT-proBNP†, *n* (%)	12 (17.9)	124 (41.6)	73 (62.9)	36.113§	<0.001
Medication, *n* (%)					
Oral anticoagulation	5 (7.5)	29 (9.7)	11 (9.5)	0.335§	0.846
Aspirin	13 (19.4)	107 (35.9)	62 (53.5)	22.172§	<0.001
Statins	8 (11.9)	91 (30.5)	50 (43.1)	19.361§	<0.001
β-blocker	19 (28.4)	126 (42.3)	61 (52.6)	10.277§	0.006
Calcium channel blocker	7 (10.5)	93 (31.2)	54 (46.6)	25.669§	<0.001
ACEI/ARB	14 (20.9)	164 (55.0)	71 (61.2)	30.987§	<0.001
Digoxin	0	7 (2.4)	12 (10.3)	17.271§	<0.001
Diuretic	3 (4.5)	30 (10.1)	24 (20.7)	13.070§	0.002
Class I antiarrhythmic	7 (10.5)	34 (11.4)	21 (18.1)	3.746§	0.154
Amiodarone	6 (9.0)	49 (16.4)	18 (15.5)	2.396§	0.302

Values are present by median (Q_1, Q_3) or *n* (%); *LAD ≥35 mm for women or ≥40 mm for men; †NT-proBNP ≥400 pg/ml; ‡Wilcoxon rank-sum test; §Chi-square test. SSS: Sick sinus syndrome; ACEI/ARB: Angiotensin converting enzyme inhibitors/angiotensin II receptor blocker; AF: Atrial fibrillation; LAD: Left atrial diameter; MI: Myocardial infarction; NT-proBNP: Amino-terminal pro-brain natriuretic peptide; TE: Thromboembolism; TIA: Transient ischemic attack.

Table 3: Relationship between left atrial diameter and NT-proBNP and the outcomes of stroke and death

Events	Univariate analysis			Multivariate analysis		
	HR	95% *CI*	*P*	*HR*	95% *CI*	*P*
Stroke						
Increased LAD	3.94	1.90–8.16	<0.001	4.20	1.83–9.62	<0.001
Increased NT-proBNP	2.02	1.06–3.85	0.033	1.26	0.63–2.52	0.508
Death						
Increased LAD	1.68	0.92–3.07	0.089	1.11	0.53–2.32	0.774
Increased NT-proBNP	3.49	1.83–6.69	<0.001	1.82	0.90–3.69	0.095

Multivariate analysis was adjusted by age, sex, AF history, type of pacemakers, oral anticoagulation and aspirin administration, the presence of congestive heart failure, hypertension, diabetes, previous stroke/TIA/TE and vascular disease. LAD: Left atrial diameter; NT-proBNP: Amino-terminal pro-brain natriuretic peptide; Increased LAD: LAD ≥35 mm for women or ≥40 mm for men; Increased NT-proBNP: NT-proBNP ≥400 pg/ml; *CI*: Confidence interval; *HR*: Hazard ratio; AF: Atrial fibrillation.

0.66, 95% *CI* 0.57–0.74, *P* = 0.013), but not for death. Conversely, the combination of increased NT-proBNP and the CHA2DS2-VASc score showed improved predictive power for death (C-stat 0.70, 95% *CI* 0.64–0.77 vs. C-stat 0.67, 95% *CI* 0.60–0.75, *P* = 0.023), but not for stroke [Table 5 and Figure 2]. The addition of both increased LAD and increased NT-proBNP to the CHA2DS2-VASc score tended to improve the ability to predict stroke and death, but the difference was not statistically significant.

Discussion

In this population of patients with SSS and implanted pacemakers, our principle findings were that the CHA2DS2-VASc score is valuable for predicting the risk

Table 4: Association of CHA2DS2-VASc score and CHA2DS2-VASc score adding increased LAD, increased NT-proBNP, or both with outcomes of stroke and death

Scores	Stroke			Death		
	HR	95% *CI*	*P*	*HR*	95% *CI*	*P*
CHA2DS2-VASc score	1.45	1.20–1.75	<0.001	1.45	1.22–1.71	<0.001
Plus increased LAD	1.50	1.26–1.78	<0.001	1.41	1.21–1.65	<0.001
Plus increased NT-proBNP	1.43	1.20–1.70	<0.001	1.48	1.26–1.73	<0.001
Plus increased LAD and NT-proBNP	1.46	1.24–1.71	<0.001	1.43	1.23–1.66	<0.001

LAD: Left atrial diameter; NT-proBNP: Amino-terminal pro-brain natriuretic peptide; *CI*: Confidence interval; *HR*: Hazard ratio.

Table 5: Predictive values of the CHA2DS2-VASc score adding increased LAD, increased NT-proBNP, or both for the prediction of stroke and death

Scores	Stroke			Death		
	AUC	95% *CI*	*P**	*HR*	95% *CI*	*P**
CHA2DS2-VASc score	0.66	0.57–0.74	–	0.67	0.60–0.75	–
Plus increased LAD	0.69	0.61–0.77	0.013	0.68	0.60–0.75	0.976
Plus increased NT-proBNP	0.67	0.58–0.75	0.443	0.70	0.64–0.77	0.023
Plus increased LAD and NT-proBNP	0.69	0.61–0.77	0.075	0.70	0.63–0.77	0.206

**P*: Comparing the CHA2DS2-VASc score with the score plus increased LAD, increased NT-proBNP or both using DeLong test. LAD: Left atrial diameter; NT-proBNP: Amino-terminal pro-brain natriuretic peptide; *CI*: Confidence interval; *HR*: Hazard ratio; AUC: Area under the curve.

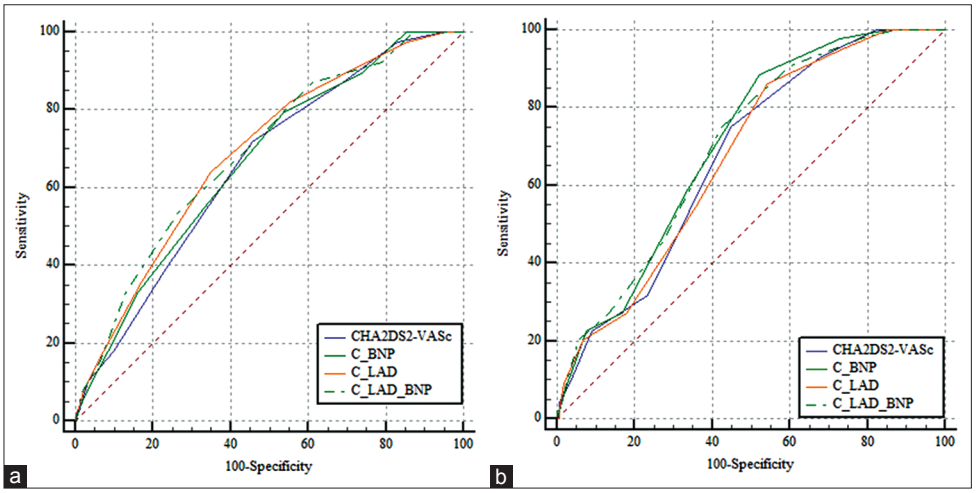

Figure 2: Receiver operating characteristic curves of adding increased LAD, increased NT-proBNP, or both to the CHA2DS2-VASc score for the prediction of stroke (a) and death (b). C_BNP: CHA2DS2-VASc score plus increased NT-proBNP, C_LAD: CHA2DS2-VASc score plus LAD; C_LAD_BNP: CHA2DS2-VASc score plus increased NT-proBNP and increased LAD; LAD: Left atrial diameter; NT-proBNP: Amino-terminal pro-brain natriuretic peptide.

of stroke and death in Chinese patients with SSS after pacemaker implantation and that the addition of LAD and NT-proBNP to the CHA2DS2-VASc score improved the predictive value for stroke and death, respectively.

The CHA2DS2-VASc score is a risk prediction tool that was derived from and validated in AF populations.[9] In this study, the CHA2DS2-VASc score was found to be significantly associated with stroke and death in patients with SSS after pacemaker implantation. A previous study of 1415 patients with SSS and pacemakers from the DANPACE trial demonstrated a similar predictive value of the risk score regarding stroke and death.[8] In that study, the incidence of stroke increased by 1.25 times and the incidence of death increased by 1.39 times for every one point increase. Our study confirmed the predictive value of the CHA2DS2-VASc score for stroke and death in Chinese patients paced for SSS.

In another non-AF population, the CHA2DS2-VASc score was also reported to have predictive capacity for stroke and death. In 20,970 patients with acute coronary syndromes, Mitchell *et al*.[7] found that the incidence of stroke and death was significantly positively related to the CHA2DS2-VASc score over a median follow-up of 4.1 years. Moreover, a recent study of 42,987 patients with HF showed that among patients with HF with or without AF, the CHA2DS2-VASc score was associated with the risk of ischemic stroke, thromboembolism, and death.[4] In a study of 3492 patients

who underwent cardiac surgery, the development of stroke was associated with a higher CHA2DS2-VASc score, and multivariable analysis showed that the CHA2DS2-VASc score was an independent predictor of postoperative strokes.[6] The Chin-Shan Community Cohort Study from Taiwan found that the CHA2DS2-VASc score could be even applied to the general population with a modest predictive value.[14]

The reason why the CHA2DS2-VASc score is useful to predict stroke in non-AF patients is easy to understand since the components of the CHA2DS2-VASc score include the risk factors of stroke, independent of AF. The CHA2DS2-VASc score also includes the main risk factors for AF,[15] indicating that patients with higher scores are more likely to develop AF,[16,17] which leads to an increased risk of stroke. The CHA2DS2-VASc score was not initially designed to predict the risk of death. However, it turned out that the score did quite well in predicting death events, which may be due to the fact that the scoring parameters consist of cardiovascular risk factors.

However, the discrimination capability of the CHA2DS2-VASc score was found to be modest in the AF population,[9] as well as in the non-AF population.[4-8] Factors beyond the components of the CHA2DS2-VASc score, such as impaired renal function, obstructive sleep apnea, and echocardiographic and biochemical parameters, were found to predict adverse thromboembolic events in the AF population.[10] LAD and NT-proBNP are simple variables that are widely used in daily clinical practice. In this study, we sought to improve the predictive ability of the CHA2DS2-VASc score by adding those two simple parameters to keep the score easy to evaluate. The results showed that adding LAD improved the predictive ability for stroke while adding NT-proBNP improved the predictive ability for death.

LAD by transthoracic echocardiography is the simplest assessment approach among the variables of left atrial structure and function. Hamatani *et al*.[11] defined left atrial enlargement as LAD >45 mm and demonstrated that in patients with AF, left atrial enlargement was an independent predictor of stroke/systemic embolism. Moreover, in patients with AF, adding left atrial volume to the CHA2DS2-VASc score was shown to significantly improve the predictive power for the presence of left atrial thrombus or dense spontaneous echo contrast.[12] In the present study, we found that LAD was an independent risk factor of stroke and that adding LAD to the CHA2DS2-VASc score improved the predictive power for stroke in patients with SSS after pacemaker implantation. Left atrial enlargement can promote blood stasis and patients with larger left atria are likely to develop AF,[18] which may explain the association between LAD and stroke.

NT-proBNP is a recognized marker of myocardial wall tension, such as volume or pressure overload. It has been reported to be a marker of increased mortality in congestive HF, ischemic heart disease, and also community-based healthy subjects.[19] In patients with AF, NT-proBNP was independently related to increased risks of stroke and death[20] and was proven to provide complementary prognostic information to the CHA2DS2-VASc score for the prediction of stroke and death.[13] In this study, we found that adding NT-proBNP to the CHA2DS2-VASc score significantly improved the prediction of death in patients with SSS and implanted pacemakers.

As the CHA2DS2-VASc score has been proven effective in the non-AF population with a modest discriminatory power, our results suggest that the addition of LAD and NT-proBNP to enhance the CHA2DS2-VASc score might be an effective strategy. Future prospective studies are warranted to confirm the value of adding LAD and NT-proBNP to the CHA2DS2-VASc score for the improved prediction of stroke and death risk.

There were several limitations in this study. This study was performed in a very specific population of patients with SSS after pacemaker implantation, which may limit the generalization. We have only recorded a unique value of LAD and NT-proBNP before pacemaker implantation rather than after pacemaker implantation, and changes may have occurred during follow-up. The specificity of diagnosing AF according to the medical records, ECG, and Holter at baseline was not sufficiently high. Thus, patients with silent AF may have been misclassified as non-AF patients, and patients who were classified into the non-AF group at baseline may have experienced new-onset AF during follow-up. Due to the retrospective design, data on new-onset AF were not collected over time in this study. Pacemaker-detected AF episodes were not evaluated since none of the VVI pacemakers and not all of the DDD pacemakers have this function. Information regarding the use of warfarin was only available in patients who took warfarin at baseline, and these patients were simply classified into a regular use group and an irregular use group as the international normalized ratio values during follow-up were not independently monitored.

To conclude, in Chinese patients with SSS after pacemaker implantation, the CHA2DS2-VASc score is predictive of the risk of stroke and death. Adding LAD and NT-proBNP to the CHA2DS2-VASc score improved the predictive value of stroke and death, respectively. Future prospective studies are warranted to confirm the value of adding LAD and NT-proBNP to the CHA2DS2-VASc score in predicting stroke and death risk in non-AF populations.

Financial support and sponsorship

This work was supported by grants from the State Key Program of National Natural Science Foundation of China (No. 81530015), National Natural Science Foundation of China grant (No. 81270258), and Shanghai City Committee of Science and Technology Research Projects (Nos. 12411951900, 13140903801, and 14441902502).

Conflicts of interest

There are no conflicts of interest.

References

1. Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, *et al.* Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133 6 Suppl:546S-92S. doi: 10.1378/chest.08-0678.
2. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, *et al.* 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719-47. doi: 10.1093/eurheartj/ehs253.
3. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., *et al*. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1-76. doi: 10.1016/j.jacc.2014.03.022.
4. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY, *et al.* Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. JAMA 2015;314:1030-8. doi: 10.1001/jama.2015.10725.
5. Biancari F, Asim Mahar MA, Kangasniemi OP. CHADS2 and CHA2DS2-VASc scores for prediction of immediate and late stroke after coronary artery bypass graft surgery. J Stroke Cerebrovasc Dis 2013;22:1304-11. doi: 10.1016/j.jstrokecerebrovasdis.2012.11.004.
6. Peguero JG, Issa O, Podesta C, Elmahdy HM, Santana O, Lamas GA, *et al.* Usefulness of the CHA2DS2VASc score to predict postoperative stroke in patients having cardiac surgery independent of atrial fibrillation. Am J Cardiol 2015;115:758-62. doi: 10.1016/j.amjcard.2014.12.037.
7. Mitchell LB, Southern DA, Galbraith D, Ghali WA, Knudtson M, Wilton SB, *et al.* Prediction of stroke or TIA in patients without atrial fibrillation using CHADS2 and CHA2DS2-VASc scores. Heart 2014;100:1524-30. doi: 10.1136/heartjnl-2013-305303.
8. Svendsen JH, Nielsen JC, Darkner S, Jensen GV, Mortensen LS, Andersen HR, *et al.* CHADS2 and CHA2DS2-VASc score to assess risk of stroke and death in patients paced for sick sinus syndrome. Heart 2013;99:843-8. doi: 10.1136/heartjnl-2013-303695.
9. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. Chest 2010;137:263-72. doi: 10.1378/chest.09-1584.
10. Szymanski FM, Lip GY, Filipiak KJ, Platek AE, Hrynkiewicz-Szymanska A, Opolski G. Stroke risk factors beyond the CHA(2)DS(2)-VASc score: Can we improve our identification of "high stroke risk" patients with atrial fibrillation? Am J Cardiol 2015;116:1781-8. doi: 10.1016/j.amjcard.2015.08.049.
11. Hamatani Y, Ogawa H, Takabayashi K, Yamashita Y, Takagi D, Esato M, *et al.* Left atrial enlargement is an independent predictor of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Sci Rep 2016;6:31042. doi: 10.1038/srep31042.
12. Kim MN, Kim SA, Choi JI, Park SM, Park SW, Kim YH, *et al.* Improvement of predictive value for thromboembolic risk by incorporating left atrial functional parameters in the CHADS2 and CHA2DS2-VASc scores. Int Heart J 2015;56:286-92. doi: 10.1536/ihj.14-380.
13. Roldán V, Vílchez JA, Manzano-Fernández S, Jover E, Gálvez J, Puche CM, *et al.* Usefulness of N-terminal pro-B-type natriuretic peptide levels for stroke risk prediction in anticoagulated patients with atrial fibrillation. Stroke 2014;45:696-701. doi: 10.1161/strokeaha.113.003338.
14. Lip GY, Lin HJ, Chien KL, Hsu HC, Su TC, Chen MF, *et al*. Comparative assessment of published atrial fibrillation stroke risk stratification schemes for predicting stroke, in a non-atrial fibrillation population: The Chin-Shan Community Cohort Study. Int J Cardiol 2013;168:414-9. doi: 10.1016/j.ijcard.2012.09.148.
15. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr., *et al.* Development of a risk score for atrial fibrillation (Framingham heart study): A community-based cohort study. Lancet 2009;373:739-45. doi: 10.1016/s0140-6736(09)60443-8.
16. Sciacqua A, Perticone M, Tripepi G, Tassone EJ, Cimellaro A, Mazzaferro D, *et al.* CHADS2 and CHA2DS2-VASc scores are independently associated with incident atrial fibrillation: The catanzaro atrial fibrillation project. Intern Emerg Med 2015;10:815-21. doi: 10.1007/s11739-015-1243-3.
17. Yang Y, Zhang Z, Ng CY, Li G, Liu T. Meta-analysis of CHADS2 score in predicting atrial fibrillation. Am J Cardiol 2015;116:554-62. doi: 10.1016/j.amjcard.2015.05.010.
18. Sciacqua A, Perticone M, Tripepi G, Miceli S, Tassone EJ, Grillo N, *et al.* Renal disease and left atrial remodeling predict atrial fibrillation in patients with cardiovascular risk factors. Int J Cardiol 2014;175:90-5. doi: 10.1016/j.ijcard.2014.04.259.
19. Di Angelantonio E, Chowdhury R, Sarwar N, Ray KK, Gobin R, Saleheen D, *et al.* B-type natriuretic peptides and cardiovascular risk: Systematic review and meta-analysis of 40 prospective studies. Circulation 2009;120:2177-87. doi: 10.1161/circulationaha.109.884866.
20. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, *et al.* Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: A randomized evaluation of long-term anticoagulation therapy (RE-LY) substudy. Circulation 2012;125:1605-16. doi: 10.1161/circulationaha.111.038729.