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The CHA2DS2-VASc Score A Predictor of Thromboembolic Events and Mortality In Patients With an Implantable Monitoring Device Without Atrial Fibrillation

Christine Parsons, MD¹, Salma I. Patel, MD, MPH¹, Stephen Cha, MS², Win-Kuang Shen, MD³, Santosh Desai, DO³, Alanna M. Chamberlain, PhD⁴, Sushil Allen Luis, MBBS, FRACP⁵, Maria I. Aguilar, MD⁶, Bart M. Demaerschalk, MD, MSc, FRCPC⁶, Farouk Mookadam, MB, BCh, MSc³, and Fadi Shamoun, MD³

¹Department of Internal Medicine, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ, USA 85259

²Department of Health Science Research, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ, USA 85259

³Division of Cardiovascular Diseases, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ, USA 85259

⁴Department of Health Sciences Research, Mayo Clinic, 200 1st St SW, Rochester, MN, USA 55905

⁵Division of Cardiovascular Diseases, Mayo Clinic, 200 1st St SW, Rochester, MN, USA 55905

⁶Department of Neurology, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ, USA 85259

Abstract

Objective—To determine if the CHA2DS2-VASc score predicts thromboembolism and death in patients without atrial fibrillation in a population with implantable cardiac monitoring devices.

Methods—A retrospective review utilizing the Rochester Epidemiology Project research infrastructure was conducted to evaluate the CHA2DS2-VASc tool as a predictor of mortality and ischemic stroke, transient ischemic attack, or systemic embolism in patients without atrial fibrillation. An implantable device was required in the inclusion criteria to discern the absence of atrial fibrillation. The study period was January 1, 2004 through March 7, 2016.

Results—The population (n = 1,606) had a mean age of 69.8 years (SD 3.4 years) and median follow-up of 4.8 years (range 0 to 12 years, Q1: 2.6 years, Q3: 8.1 years). The number of thromboembolic and mortality events stratified by CHA2DS2-VASc score groupings of 0 to 2, 3 to

Corresponding author: Fadi Shamoun, MD, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ, USA 85259, Shamoun.Fadi@mayo.edu, Phone: (480) 301-6201, Fax: (480) 301-8018.

DISCLOSURES

Alanna M. Chamberlain is a Co-Investigator of the Rochester Epidemiology Project. The authors have no other conflicts of interest to declare.

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5, and 6 to 9 were 12 (3%), 109 (14%), and 123 (27%); and 22 (6%), 205 (27%), and 214 (47%), respectively. The CHA2DS2-VASc score predicted thromboembolism and death. The hazard ratios for thromboembolic events for CHA2DS2-VASc scores 3 to 5 and 6 to 9 were 4.84 (CI 2.66 to 8.80) and 10.53 (CI 5.77 to 19.21) (reference group: scores 0 to 2). The hazard ratios for death for the corresponding score categories were 4.45 (CI 2.86 to 6.91) and 8.18 (CI 5.23 to 12.78). The CHA2DS2-VASc score also predicted development of atrial fibrillation, where the hazard ratios for scores 3 to 5 and 6 to 9 were 1.51 (CI 1.13 to 2.00) and 2.17 (CI 1.60 to 2.95).

Conclusion—The CHA2DS2-VASc tool predicts thromboembolic events and overall mortality in those without atrial fibrillation in a population with implantable devices.

Keywords

CHA2DS2-VASc score; thromboembolism; anticoagulation; atrial fibrillation

Journal Subject Terms

Atrial fibrillation; Risk Factors; Anticoagulants; Embolism

INTRODUCTION

The CHA2DS2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category) score is a validated tool to predict the risk of stroke and systemic emboli in patients with non-valvular atrial fibrillation.^{1–4} The CHA2DS2-VASc score is recommended for assessment of systemic emboli risk in patients with non-valvular atrial fibrillation and oral anticoagulation is recommended for those patients with a score of 2 or greater.⁵ Treatment with an oral anticoagulant or aspirin in this population may be considered for a CHA2DS2-VASc score of 1.⁵ Given these 2014 AHA/ACC/HRS guidelines, the use of CHA2DS2-VASc in determining the need for anticoagulation in non-valvular atrial fibrillation has become standard practice.

The components of the CHA2DS2-VASc score have been shown separately to represent significant risk factors for embolism, with certain elements such as prior stroke or TIA and age carrying particular weight.^{6–9} Although the thromboembolic predictive value of CHA2DS2-VASc in populations without atrial fibrillation is less established, the individual components are associated with an increased incidence of systemic emboli and mortality, in both atrial fibrillation and non-atrial fibrillation patients with prior stroke.^{10–14}

The aim of the present study was to determine the association between the CHA2DS2-VASc score and mortality, ischemic stroke, TIA, or systemic embolism in patients without atrial fibrillation as assessed by a pacemaker, implantable cardiac defibrillator (ICD) or loop recorder in the Olmsted County, Minnesota population. The development of atrial fibrillation and the effect of anticoagulation and prior renal impairment were also of interest. Renal impairment was evaluated as research has shown that renal dysfunction in atrial fibrillation patients represents a high-risk group for systemic thromboembolic events, however, studies

have been conflicting whether kidney function should be incorporated in risk stratification.^{15–17}

METHODS

The study is a retrospective review utilizing the Rochester Epidemiology Project (REP), which links and indexes the medical records of Olmsted County residents.¹⁸ The study was approved by the Olmsted Medical Center Institutional Review Board (IRB) and the Mayo Clinic IRB. This study was considered minimal risk by the IRBs; therefore, the requirement for informed consent was waived. The records of any patient who did not provide authorization for their medical records to be used for research, as per Minnesota statute (Statute 144.335), were not included.

We identified all subjects that had an implantable pacemaker, defibrillator or loop recorder placed between January 1, 2004 and December 31, 2013, where the index date (time zero) was defined as the date of device implantation. The presence of any atrial fibrillation was assessed by cardiac implanted devices, which allow continuous and accurate monitoring of heart rhythms such as atrial fibrillation.¹⁹ The presence of a cardiac implanted electronic device was an inclusion criterion for the study in order to provide objective evidence that the population evaluated does not have significant atrial fibrillation burden. Follow-up was defined as the time to first thromboembolic event, death or the end of the study period (which was the time of data collection, March 7, 2016). Subjects were older than 50 years and had no diagnosis of atrial fibrillation before the index date. Figure 1 describes the process for generating the cohort.

A total of 3,033 patients were identified as having a qualifying implantable device and 1,427 of these patients were removed as they had an International Classification of Diseases, Ninth Revision, (ICD-9) diagnosis of atrial fibrillation prior to device implantation. Thus, 1,606 subjects met inclusion criteria. ICD-9 diagnostic codes were used to identify the CHA2DS2-VASc variables at the index date and as they developed over time. The International Classification of Diseases is the official system of assigning codes to diagnoses associated with hospital utilization in the United States and is based on the World Health Organization's International Classification of Diseases.

ICD-9 diagnostic code sets were developed for the CHA2DS2-VASc components of congestive heart failure, hypertension, diabetes mellitus, ischemic stroke, and TIA. ICD-9 codes for coronary artery disease, angina, ischemic heart disease, and peripheral vascular disease were utilized to comprise a code set for vascular disease. Renal impairment and the development of atrial fibrillation were also identified using ICD-9 diagnostic codes. Renal impairment was defined as end stage renal disease, dialysis, or chronic kidney disease stage III or greater. Prescriptions for oral anticoagulation (warfarin, dabigatran, apixaban, or rivaroxaban) were also obtained. Outpatient prescriptions were obtained from Mayo Clinic and Olmsted Medical Center, converted into RxNorm codes, and subsequently grouped using the National Drug-File Reference Terminology.²⁰ The primary outcome was defined as the first thromboembolic event including ischemic stroke, TIA, or systemic emboli that was diagnosed using ICD-9 codes after the index date through March 7, 2016. A random

sample of thromboembolic events in the identified population was verified by manual chart review and 100% of these were found to represent true outcomes. Survival was a secondary outcome, identified from inpatient and outpatient medical records, death certificates from the state of Minnesota, and obituaries and notices of death in the local newspapers.

The baseline CHA2DS2-VASc score including its individual components, renal impairment, and oral anticoagulation use were recorded for each subject. Baseline characteristics and baseline CHA2DS2-VASc scores were taken at the index date (corresponding to date of cardiac monitoring device implantation or time zero). The CHA2DS2-VASc score components and oral anticoagulation use were also recorded as time dependent variables after the index date.²¹ Subjects were classified into subgroups according to the following baseline CHA2DS2-VASc scores: 0 to 2, 3 to 5, and 6 to 9. Events stratified by CHA2DS2-VASc score were evaluated by Kaplan-Meier curves and were compared using a Log-Rank test. Multivariate modeling of thromboembolic events and survival was done using Cox proportional hazard models. A p-value less than .05 was considered as statistically significant. Hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) were generated for CHA2DS2-VASc scores 3 to 5 and 6 to 9 with the CHA2DS2-VASc score 0 to 2 used as the reference group. All statistical analyses were performed using SAS version 9.4 software (SAS institute Inc. Cary NC).

RESULTS

The baseline characteristics of the cohort are described in Table 1. Subjects had a mean age of 69.8 years (standard deviation (SD) 3.4 years, range 50 to 99 years) and median follow-up of 4.8 years (range 0 to 12 years, quartile (Q) 1: 2.6 years, Q3: 8.1 years). The subsequent development of CHA2DS2-VASc score components among the cohort that were not present at the date of device implantation is shown in Table 2.

Death and thromboembolic event incidence by CHA2DS2-VASc score is shown in Figure 2a and 2b. The number of thromboembolic events and overall mortality events stratified by CHA2DS2-VASc score groupings of 0 to 2, 3 to 5, and 6 to 9 were 12, 109, and 123; and 22, 205, and 214, respectively. Cumulative mortality at 6 months and at 5 years for CHA2DS2-VASc scores 0 to 2, 3 to 5, and 6 to 9 was 1.5% (CI 0.3 to 2.7), 2.5% (CI 1.4 to 3.6), and 5.8% (CI 3.6 to 7.9); and 4.4% (CI 2.2 to 6.6), 19.3% (CI 16.1 to 22.4), and 34.3% (CI 29.3 to 38.1), respectively. Cumulative incidence of thromboembolism at 6 months and at 5 years for CHA2DS2-VASc scores 0 to 2, 3 to 5, and 6 to 9 was 0.5% (CI 0.0 to 1.2), 3.9% (CI 2.5 to 5.3), and 8.2% (CI 5.6 to 10.8); and 1.9% (CI 0.5 to 3.3), 14.1% (CI 11.2 to 17.0), and 29.4% (CI 24.4 to 34.2), respectively.

Development of atrial fibrillation by CHA2DS2-VASc score grouping is shown in Figure 2c. The number of patients that developed atrial fibrillation stratified by CHA2DS2-VASc score groupings of 0 to 2, 3 to 5, and 6 to 9 was 65, 185, and 144. The cumulative incidence of atrial fibrillation at 6 months and at 5 years for CHA2DS2-VASc scores 0 to 2, 3 to 5, and 6 to 9 was 4.8% (CI 2.7 to 6.9), 7.5% (CI 5.6 to 9.4), and 6.9% (CI 4.5 to 9.2); and 13.2% (CI 9.6 to 16.8), 23.6% (CI 20.1 to 26.9), and 31.7% (CI 26.4 to 36.7), respectively.

The HRs for death for CHA2DS2-VASc scores 3 to 5 and 6 to 9 (using scores 0 to 2 as the reference group) were 4.45 (95% CI 2.86 to 6.91) and 8.18 (95% CI 5.23 to 12.78), respectively (Table 3). After adjusting other covariates (as shown in Table 3), the HRs for thromboembolic events for CHA2DS2-VASc scores 3 to 5 and 6 to 9 were 4.84 (95% CI 2.66 to 8.80) and 10.53 (95% CI 5.77 to 19.21), respectively. These results were maintained with a 0 to 1 reference group as well: mortality HRs were 4.86 (95% CI 2.49 to 9.48) and 10.22 (95% CI 5.21 to 20.04), and thromboembolism HRs were 3.44 (95% CI 1.60 to 7.39) and 8.96 (95% CI 4.15 to 19.36) for CHA2DS2-VASc scores 2 to 5 and 6 to 9, respectively. The CHA2DS2-VASc score in general provided incremental prediction over the individual components as shown in Supplemental Table 1.

The HRs for development of atrial fibrillation for CHA2DS2-VASc scores 3 to 5 and 6 to 9 were 1.51 (95% CI 1.13 to 2.00) and 2.17 (95% CI 1.60 to 2.95), respectively. Those that developed atrial fibrillation had a HR for death of 2.35 (95% CI 1.86 to 2.97) and a HR for thromboembolic events of 1.99 (95% CI 1.39 to 2.84). Anticoagulation after index date had a HR for death of 0.92 that was not significant (95% CI 0.69 to 1.22, $P=.55$). Anticoagulation after index date had a HR for thromboembolic events of 0.77, which also was not significant (95% CI 0.47 to 1.28, $P=.32$). The subpopulation initiated on oral anticoagulation after index date was small ($n=228$). The HR for death for those with renal impairment at the index date was 1.92 (95% CI 1.53 to 2.42) and the HR for thromboembolic events was not significant (HR 1.25, 95% CI 0.90 to 1.75, $P=.19$).

The HRs for outcomes of interest based on development of CHA2DS2-VASc components after the index date are shown in Table 4. Incident thromboembolism had the largest HR for mortality (HR 2.35, 95% CI 1.78 to 3.10). Incident heart failure had a HR for mortality of 1.88 (95% CI 1.47 to 2.41). Development of hypertension after the index date was the greatest risk factor for thromboembolic events (HR 2.58, 95% CI 1.51 to 4.39). Incident heart failure was the best predictor of atrial fibrillation out of evaluated variables (HR 2.96, 95% CI 2.19 to 4.00). The only other variable that was significantly predictive of atrial fibrillation was diabetes mellitus (HR 1.42, 95% CI 1.04 to 1.96).

Counts of patients with a loop recorder, pacemaker, or ICD were 659, 778, and 169, respectively. Sub-analysis stratifying by implantable device type showed that the relationship between CHA2DS2-VASc score and thromboembolic and mortality outcomes was maintained across all device types although results were not significant for the ICD group likely secondary to the small sample size (Supplemental Tables 2, 3 and 4). Multivariate modeling including device type showed that patients with a loop recorder or ICD had HRs 0.31 (95% CI 0.24 to 0.41) and 0.66 (95% CI 0.48 to 0.88) compared to those with a pacemaker. Patients with an ICD had a HR of 1.78 (95% CI 1.29 to 2.46) compared to those with loop recorder.

DISCUSSION

The CHA2DS2-VASc score is a well-validated tool for predicting thromboembolism and initiating anticoagulation in populations with atrial fibrillation. The CHA2DS2-VASc score has been evaluated by several studies in prior stroke patients without atrial fibrillation. A 5-

year prospective study found that the CHA2DS2-VASc score predicts long-term stroke outcomes in first-time ischemic stroke patients without atrial fibrillation.¹⁴ A study of ischemic stroke patients found that the pre-stroke CHA2DS2-VASc score has high sensitivity for estimating 3-month stroke outcomes in both patients with and without atrial fibrillation.²² In a population of stroke patients with heart failure, early and late stroke outcome was not associated with the presence of atrial fibrillation.¹²

Subclinical atrial fibrillation may contribute to the above observation that the CHA2DS2-VASc score was predictive of thromboembolism in certain patient groups without atrial fibrillation. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial found that device-detected atrial tachyarrhythmias lasting longer than six minutes were associated with an increased risk of systemic embolism.²³ The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk study and subgroup analysis of the Mode Selection Trial also reported increased thromboembolic events with device-detected atrial tachyarrhythmias.^{24, 25} Further analysis of the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial indicated that there was not a strong temporal relationship of the tachyarrhythmia to the thromboembolic event (only 8% of patients had subclinical atrial fibrillation detected within 30 days before the thromboembolic event).²⁶

Research indicates that atrial fibrillation carries stroke risk regardless of whether or not it is sustained.²⁷ The burden of atrial fibrillation detected by cardiac implanted electronic devices predicts ischemic stroke.²⁸ There is also an apparent correlate between atrial fibrosis and the persistence and burden of atrial fibrillation.²⁷ Atrial fibrosis and associated inflammation may contribute to both the pathophysiology of atrial fibrillation and thromboembolism and perhaps explain why atrial fibrillation does not necessarily precede embolic events.^{29–32} In a study of paroxysmal atrial fibrillation patients who underwent ablation, latent high coagulation activity in the left atrium was observed.³⁰ This was significantly lower in patients on warfarin. Ablation does not halt fibrosis progression; suggesting inflammation is not solely the result of atrial fibrillation.³³ A prospective study found that CHADS2 score correlated with higher left atrial fibrosis in atrial fibrillation patients, and atrial fibrosis independently predicted cerebrovascular events and significantly increased the predictive performance of the score.³⁴ Atrial inflammation possibly may be assessed by risk factors encompassed within the CHA2DS2-VASc score. An association has been noted between inflammatory parameters and CHA2DS2-VASc score in patients with non-valvular atrial fibrillation.³⁵

The present retrospective review finds that the CHA2DS2-VASc score predicted thromboembolic events in those without atrial fibrillation as evaluated by cardiac implantable electronic devices. This is consistent with studies of prior stroke patients as described. This is the first study to our knowledge that evaluates the CHA2DS2-VASc score in patients without atrial fibrillation that is not limited to patients with a prior history of stroke or heart failure. The CHA2DS2-VASc score also predicted all-cause mortality in patients without atrial fibrillation, which is expected given the increased incidence of thromboembolic events and the increased comorbidities inherent in the score calculation.

Our results align with those of the few studies that have evaluated the relation of CHA2DS2-VASc score to death irrespective of the presence of atrial fibrillation.^{14, 36}

Incident thromboembolism and heart failure were most associated with mortality of the evaluated variables that developed after the index date. Incident hypertension was associated with thromboembolic events. The few studies evaluating the utility of the CHA2DS2-VASc score in populations without atrial fibrillation have not commented specifically on the relation of incident CHA2DS2-VASc components to thromboembolic and mortality outcomes. In a retrospective study evaluating the CHADS2 score, baseline age followed by heart failure then previous stroke were the components that had the highest impact on all-cause mortality in patients with and without documented atrial fibrillation.¹¹ A study in congestive heart failure patients without atrial fibrillation found that all baseline CHA2DS2-VASc components were independently associated with ischemic stroke.³⁶

The incidence of thromboembolism and death was substantial, particularly with CHA2DS2-VASc scores greater than 2. The percentages of patients suffering a thromboembolic event during the study period for CHA2DS2-VASc scores 0 to 2, 3 to 5, and 6 to 9 were 3%, 14%, 27%. However, the study period extended greater than 10 years, perhaps partially accounting for the high incidence. The incidence of thromboembolic events in the overall population by 3 months was 3.0%. This is less than the ASSERT thromboembolism incidence at 3 months in the subclinical atrial tachyarrhythmia group (4.2%) and higher than that in the non-arrhythmia group (1.7%).²³ In a congestive heart failure population, the incidence of thromboembolism at 5 years was 16.5% in those without atrial fibrillation and 11.9% in those with atrial fibrillation compared to 12.4% at 5 years in our study.³⁶ The death incidence during the study period for CHA2DS2-VASc scores 0 to 2, 3 to 5, and 6 to 9 was 6%, 27%, and 48%. The high baseline prevalence and high incident CHA2DS2-VASc variables indicates a population with high morbidity.

Our study results also show that the CHA2DS2-VASc score predicted new onset atrial fibrillation in the population. This indicates that the components of the CHA2DS2-VASc score may impact risk for atrial fibrillation and associated thromboembolic events. Incident heart failure and diabetes mellitus were the only predictors of atrial fibrillation out of evaluated variables that developed after the index date. A large prospective study also found that CHA2DS2-VASc score predicted atrial fibrillation, and all CHA2DS2-VASc components were predictive, particularly age and heart failure.³⁷ A significant number of patients developed atrial fibrillation after device implantation in our study. As described, CHA2DS2-VASc score has been shown to correlate with atrial inflammation and therefore, this possibly underlies the association between a higher CHA2DS2-VASc score and the development of both atrial fibrillation and thromboembolism. Furthermore, there may have been an increased prevalence of undiagnosed paroxysmal atrial fibrillation preceding device implantation in study patients with high CHA2DS2-VASc scores. A lag could exist between subclinical atrial arrhythmias and clinical detection. There also may be a higher prevalence of subclinical atrial tachyarrhythmias in patients with implantable devices and high-risk groups. The ASSERT trial also found that atrial tachyarrhythmias occurred in a large percentage (10% within 3 months of device implantation) of the population, composed of patients 65 years of age or older without clinical atrial fibrillation.²³ It may be of value for

clinicians to demonstrate increased vigilance in evaluating for the presence of atrial fibrillation in patients with high CHA2DS2-VASc scores in order to facilitate anticoagulation preceding development of thromboembolism.

Although the present study did not aim to evaluate anticoagulation as an intervention, oral anticoagulation after the index date resulted in HRs of 0.92 and 0.77 for thromboembolism and death, however, these were not significant. This is likely related to the small sample size of the subpopulation. Intervention studies evaluating adverse bleeding events would be of interest and specific score cut points for anticoagulation initiation would be better established by a larger cohort.

The present study is limited in as it is a retrospective review and a larger, prospective study would yield higher evidence data. A portion of the population received oral anticoagulation (8.4% were on anticoagulation at the index date and 14.2% used anticoagulation during the study period). Anticoagulation may affect the incidence of thromboembolic events and may have lessened the risk observed with increasing CHA2DS2-VASc score. Conversely, it also may indicate unmeasured cofounders predisposing to outcome events. Antiplatelet agents were not included as part of the analysis. Just under twenty-five percent of patients developed atrial fibrillation, however, atrial fibrillation was modeled as a time dependent covariate in the statistical model to adjust the results. As shown, CHA2DS2-VASc remained predictive. There may be associated confounding variables that relate more strongly to atrial fibrillation, such as atrial inflammation. A propensity analysis for the atrial fibrillation subpopulation was not completed. Diagnosis codes were used to define atrial fibrillation, endpoints, and measured variables. These were not verified manually; including atrial fibrillation, which was not further evaluated through device interrogation reports.

CONCLUSIONS

The present retrospective review utilizing the REP medical records linkage system showed that the CHA2DS2-VASc score was an independent predictor of thromboembolic events and mortality in patients with a monitoring device and no atrial fibrillation. Increased incidence of atrial fibrillation was predicted by the CHA2DS2-VASc score and may further support consideration of anticoagulation in this population.

Anticoagulation is associated with major bleeding risks, and thus the risk of embolization needs to exceed this risk of bleeding for anticoagulation to provide net benefit. This study may help to lay the foundation for the use of anticoagulation in patients without atrial fibrillation that have a substantial risk for thromboembolic events as assessed by the CHA2DS2-VASc score. Larger prospective studies that consider bleeding risk are warranted to further investigate if the CHA2DS2-VASc score can be effectively utilized to risk stratify patients without atrial fibrillation for anticoagulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

TIA	transient ischemic attack
ICD	implantable cardiac defibrillator
REP	Rochester Epidemiology Project
IRB	institutional review board
ICD-9	International Classification of Diseases, Ninth Revision
HR	hazard ratio
CI	confidence interval
SD	standard deviation
Q	quartile

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Figure 1.

Flow diagram of the REP search to identify study sample and descriptive statistics of the study sample stratified by initial use of oral anticoagulation.

^aAnalysis was performed on entire population meeting inclusion criteria (N=1,606). Listed subgroups are for descriptive purposes.

^b228 patients (14.2%) started oral anticoagulation after device implantation.

Outcome counts reported in the 4th row were seen after a median follow-up of 4.8 years and reflect cumulative counts at the end of the study period.

Figure 2.

a. Thromboembolic events stratified by baseline CHA2DS2-VASc score in the total population. **b.** Survival stratified by baseline CHA2DS2-VASc score. **c.** Development of atrial fibrillation stratified by baseline CHA2DS2-VASc score.

Table 1

Baseline characteristics at the time of device implantation.

Variable	Overall (N=1606)	
Follow-up (years), mean $\pm$ SD	5.5 $\pm$ 3.4	
Age (years), mean $\pm$ SD	69.8 $\pm$ 12.6	
Age, n (%)		
<65	618	38%
65–74	366	23%
75+	622	39%
Gender, n (%)		
Female	872	54%
Male	734	46%
Race, n (%)		
White	1526	95%
Black	18	1%
Other	62	4%
Congestive Heart Failure, n (%)	397	25%
Hypertension, n (%)	1201	75%
Diabetes Mellitus, n (%)	682	42%
Stroke/TIA/Embolism, n (%)	464	29%
Vascular Disease, n (%)	984	61%
CHA2DS2-VASc score at baseline, n (%)		
0	52	3%
1	146	9%
2	201	13%
3	238	15%
4	280	17%
5	238	15%
6	194	12%
7	145	9%
8	85	5%
9	27	2%
Oral Anticoagulation, n (%)	136	8%
Renal Impairment, n (%)	207	13%

SD = standard deviation

Table 2

Changes in the CHA2DS2-VASc components from the index date to the end of the study.

Variable	Index Date (N=1606)		End of Study ^a (N=1606) ^b	
Age <65, n (%)	618	38%	412	25%
Age 65–74, n (%)	366	23%	572	36%
Age 75+, n (%)	622	39%	843	53%
Congestive Heart Failure, n (%)	397	25%	610	38%
Hypertension, n (%)	1201	75%	1335	83%
Diabetes Mellitus, n (%)	682	42%	969	60%
Stroke/TIA/Embolism, n (%)	464	29%	630	39%
Vascular Disease, n (%)	984	61%	1220	76%

^a Counts and prevalence percentages of variable at time of last known follow-up or end of study period. Follow-up varied across individuals with median 4.8 years (Q1: 2.6 years, Q3: 8.1 years).

^b Cumulative values were obtained by adding the number of patients who developed the variable of interest after the index date to the counts at the index date (N is the entire study population at index date) in order to demonstrate counts for development of CHA2DS2-VASc components during the study period.

Table 3

Outcome hazard ratios by CHA2DS2-VASc score and other variables.

Outcome	95% CI			
Evaluated Variable	Hazard Ratio	Lower	Upper	P-value
Death				
CHA2DS2-VASc: 3–5	4.45	(2.86,	6.91)	<.001
CHA2DS2-VASc: 6–9	8.18	(5.23,	12.78)	<.001
Anticoagulation at index date	0.71	(0.49,	1.01)	.06
Renal Impairment History	1.92	(1.53,	2.42)	<.001
Anticoagulation after index date ^a	0.92	(0.69,	1.22)	.55
Develop Atrial fibrillation ^a	2.35	(1.86,	2.97)	<.001
Thromboembolic events				
CHA2DS2-VASc: 3–5	4.84	(2.66,	8.80)	<.001
CHA2DS2-VASc: 6–9	10.53	(5.77,	19.21)	<.001
Anticoagulation at index date	1.76	(1.23,	2.51)	.002
Renal Impairment History	1.25	(0.90,	1.75)	.19
Anticoagulation after index date ^a	0.77	(0.47,	1.28)	.32
Develop Atrial fibrillation ^a	1.99	(1.39,	2.84)	<.001
Atrial fibrillation				
CHA2DS2-VASc: 3–5	1.51	(1.13,	2.00)	.005
CHA2DS2-VASc: 6–9	2.17	(1.60,	2.95)	<.001
Anticoagulation at index date	1.81	(1.30,	2.52)	<.001
Renal Impairment at index date	1.30	(0.97,	1.73)	.07
Anticoagulation after index date ^a	4.67	(3.76,	5.81)	<.001

All variables were simultaneously assessed using multivariate modeling.

^aTime dependent covariates.

Table 4

Outcome hazard ratios by changes in CHA2DS2-VASc components after the index date.

Outcome		95% CI		
Evaluated Variable	Hazard Ratio	Lower	Upper	P-value
Death				
Age 65–74	0.62	(0.40,	0.98)	.04
Age 75	0.48	(0.33,	0.70)	<.001
CHF	1.88	(1.47,	2.41)	<.001
HTN	1.54	(1.04,	2.29)	.03
DM	1.26	(0.97,	1.63)	.08
Thromboembolism	2.35	(1.78,	3.10)	<.001
Vascular disease	1.57	(1.16,	2.12)	.003
Thromboembolic events				
Age 65–74	0.76	(0.37,	1.60)	.47
Age 75	0.76	(0.45,	1.28)	.94
CHF	1.23	(0.78,	1.93)	.43
HTN	2.58	(1.51,	4.39)	.005
DM	1.37	(0.90,	2.09)	.05
Vascular disease	1.54	(0.94,	2.54)	.004
Predict atrial fibrillation				
Age 65–74	1.38	(0.91,	2.08)	.13
Age 75	1.40	(0.98,	2.00)	.06
CHF	2.96	(2.19,	4.00)	<.001
HTN	0.99	(0.61,	1.63)	.99
DM	1.42	(1.04,	1.96)	.03
Thromboembolism	1.44	(0.96,	2.17)	.08
Vascular disease	1.34	(0.93,	1.94)	.12

The table shows HRs based on the development of CHA2DS2-VASc components if absent at index date. All variables were simultaneously assessed using multivariate modeling for the reported outcomes. Baseline CHA2DS2-VASc score groupings 3–5 and 6–9, anticoagulation at index date and renal impairment history were also included in the model as variables for adjustment. All variables in the table were CHA2DS2-VASc score components, which were modeled as time dependent covariates.