Usefulness of the Addition of Renal Function to the CHA2DS2-VASc Score as a Predictor of Thromboembolism and Mortality in Patients Without Atrial Fibrillation

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Research is conflicting whether kidney function should be incorporated in thromboembolism risk prediction. Our published data showed that the CHA2DS2-VASc score predicts thromboembolism and mortality in those without atrial fibrillation. We used the Rochester Epidemiology Project medical records system to retrospectively evaluate whether adding renal impairment (1 point) to the CHA2DS2-VASc score (-R) enhances the score's prediction of mortality, thromboembolism, and atrial fibrillation in patients without atrial fibrillation. We identified patients that had an implantable cardiac monitoring device placed from January 1, 2004 to December 31, 2013, which was defined as the start date. Follow-up was through March 7, 2016. An implantable device was required to discern the absence of atrial fibrillation. Renal impairment was defined as chronic kidney disease stage 3 or greater. The population (n = 1,606) had a mean age of 69.8 years and median follow-up of 4.8 years. Baseline renal impairment was predictive of mortality (hazard ratio [HR] 2.06, 95% confidence interval [CI] 1.64 to 2.60, p <0.001), thromboembolism (HR 1.34, 95% CI 0.96 to 1.87, p = 0.09), and atrial fibrillation (HR 1.31, 95% CI 0.98 to 1.74, p = 0.07). Lower glomerular filtration rate correlated significantly with mortality. Increasing CHA2DS2-VASc-R score correlated significantly with mortality, thromboembolism, and incident atrial fibrillation. The addition of renal impairment to the CHA2DS2-VASc score improved the C-statistics for thromboembolism and survival from 0.72 to 0.73 (p = 0.01) and 0.70 to 0.72 (p <0.001). Adding renal impairment to the CHA2DS2-VASc score improves the score's prediction of thromboembolism and mortality in a population without atrial fibrillation, although the incremental benefit appears mild. © 2018 Elsevier Inc. All rights reserved. (Am J Cardiol 2018;122:597−603)

The CHA2DS2-VASc score is a well-validated tool to assess the risk of stroke and systemic emboli in patients with nonvalvular atrial fibrillation.[1,2] Atrial fibrillation confers a 6-fold increased risk of stroke[3]; however, the causality of this relation may not be as concrete as previously believed. Our recent study shows that the CHA2DS2-VASc score predicts stroke and mortality in a population without atrial fibrillation.[4] Research is conflicting whether kidney function should be incorporated in thromboembolism risk prediction tools.[5−7] The addition of renal impairment to the CHADS2 score (2 points for glomerular filtration rate [GFR] <60 ml/min) had similar predictive value to the CHADS2 and CHA2DS2-VASc scores, although notably this population excluded patients with a GFR <30.[7] The ATRIA stroke score, which includes a point for proteinuria and a point for GFR <45 ml/min, demonstrated superior stroke prediction compared with the CHA2DS2-VASc score although C-indexes were similar.[8] The present study aims to evaluate whether adding renal impairment (1 point) to the CHA2DS2-VASc score (-R) predicts thromboembolic events or mortality in a population without atrial fibrillation with implantable cardiac monitoring devices.

Methods

We conducted a retrospective review utilizing the Rochester Epidemiology Project, which links and indexes the medical records of residents in Olmsted County, Minnesota.[9] The Olmsted Medical Center and Mayo Clinic Institutional Review Boards approved the study. We identified all subjects with an implantable cardiac monitoring device (pacemaker, defibrillator, or loop recorder) placed from January 1, 2004 to December 31, 2013. The index date (time 0) was defined as the date of device implantation and follow-up was defined as the time to first thromboembolic event, death, or the end of the study period (March 7, 2016). Implantable cardiac devices allow continuous and

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accurate monitoring of dysrhythmias,[10] and were required to better exclude those with atrial fibrillation.

Inclusion criteria included age >50 years and no previous diagnosis of atrial fibrillation. A total of 1,606 subjects met inclusion criteria: 3,033 patients were identified as having a qualifying implantable device and 1,427 patients were subsequently removed as they had an International Classification of Diseases, Ninth Revision (ICD-9), diagnosis of atrial fibrillation before device implantation. Figure 1 describes the process for generating the cohort. ICD-9 diagnostic codes were used to identify the baseline subject CHA2DS2-VASc components and renal impairment. Renal impairment was defined as chronic kidney disease (CKD) stage ≥3, including end stage renal disease or dialysis. Baseline creatinine was also obtained from inpatient or outpatient laboratory records and used to calculate the GFR (ml/min/1.73 m^2) using the Modification of Diet in Renal Disease study equation. The nearest creatinine value within 1-year before or after the index date was extracted. Outpatient prescriptions for oral anticoagulation (warfarin, dabigatran, apixaban, or rivaroxaban) were obtained from Mayo Clinic and Olmsted Medical Center.

The primary outcome was thromboembolic events including ischemic stroke, transient ischemic attack, or systemic emboli which were diagnosed using ICD-9 codes. A random sample of the thromboembolic events were verified by manual chart review and 100% of these were found to represent true outcomes. Mortality and the development of atrial fibrillation were secondary outcomes. Incident atrial fibrillation was defined using ICD-9 codes and deaths were identified from inpatient and outpatient medical records, Minnesota death certificates, and obituaries and notices of death in the local newspapers. The ICD-9 codes used to define variables and outcomes are listed in the supplemental material.

The baseline CHA2DS2-VASc-R scores were calculated at the index date by adding 1 point for the presence of renal impairment to the CHA2DS2-VASc score. The number of points awarded for renal impairment in calculating the CHA2DS2-VASc-R score was determined by comparing
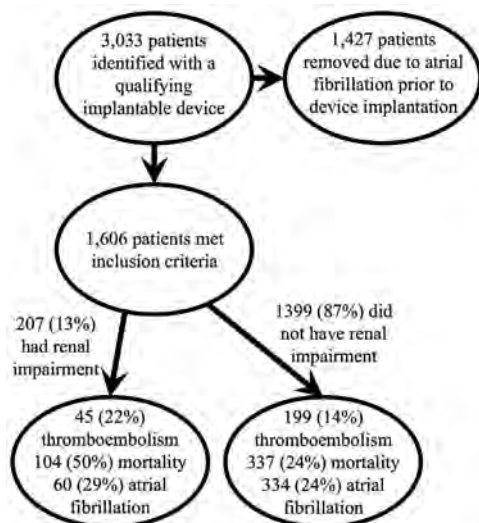
the hazard ratio (HR) of thromboembolism for renal impairment to the collective HR for various CHA2DS2-VASc scores. One point was chosen as the HRs for the various CHA2DS2-VASc scores roughly corresponded to the score value and the HR for renal impairment was 1.3. Similarly, the ATRIA stroke score assigns 1 point for renal impairment.[11] CHA2DS2-VASc-R scores were grouped as follows: 0 to 2, 3 to 6, and 7 to 10. These groupings were chosen based on similar Log-rank HRs for the subject scores within the groups.

Outcomes stratified by CHA2DS2-VASc-R score groups were evaluated using Kaplan−Meier curves and the Log-rank test. Multivariate modeling of outcomes was completed using Cox proportional hazard models. A p value <0.05 was considered as statistically significant. All statistical analyses were performed using SAS version 9.4 software (SAS institute Inc., Cary, North Carolina). The relation between baseline GFR and the study outcomes was also assessed. Baseline GFR data were grouped by CKD stages according to the 2012 Kidney Disease Improving Global Outcomes clinical practice guideline although CKD stage 3B and 3A were combined for simplicity.

Figure 1. Flow diagram of study sample identification and descriptive statistics for outcomes stratified by baseline renal impairment.

Table 1
Baseline characteristics

Variable	Overall	
	(n = 1606)	
Follow-up (years), mean ± SD	5.5	±3.4
Age (years), mean ± SD	69.8	±12.6
Women	872	(54%)
White	1526	(95%)
Black	18	(1%)
Congestive heart failure	397	(25%)
Hypertension	1201	(75%)
Diabetes Mellitus	682	(42%)
Stroke/TIA/Embolism	464	(29%)
Vascular disease	984	(61%)
Chronic kidney disease stage* (mL/min)		
1 (90+)	99	(6%)
2 (60 to 89)	589	(37%)
3 (30 to 59)	389	(24%)
4 (15 to 29)	37	(2%)
5 (<15 or Hemodialysis)	13	(1%)
Renal impairment†	207	(13%)
CHA2DS2-VASc score at baseline		
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	136	(8%)

SD = standard deviation.

* Defined by GFR data. The total number of patients with GFR data available was 1127 (70%).

† CKD stage 3 or greater defined by International Classification of Diseases, Ninth Revision codes for the total population (n = 1,606).

Results

The baseline cohort characteristics are shown in Table 1. The population (n = 1,606) had a mean age of 69.8 years (standard deviation 12.6) and mean follow-up of 5.5 years (standard deviation 3.4). There was a high degree of co-morbidity within the population as defined by a high prevalence of CHA2DS2-VASc variables (mean CHA2DS2-VASc score 4.2). Two hundred seven patients (13%) had renal impairment at baseline defined as CKD stage 3 or greater by ICD-9 codes. The total number of patients for which there was available GFR lab data within 1-year of the study start date was 1127 (70%). Those with baseline renal impairment as defined by ICD-9 codes had greater Kaplan−Meier estimates of thromboembolism (31%), mortality (57%), and atrial fibrillation (43%) at 7-years of follow-up compared with those without renal impairment (17%, 26%, and 28%, respectively) with Log-rank p <0.0001.

Table 2 shows the associated risk of incident outcomes for CHA2DS2-VASc scores 2 to 5 and 6 to 9 (CHA2DS2-VASc score 0 to 1 is the comparison), renal impairment, and anticoagulation. Renal impairment as a single variable was predictive of mortality (HR 2.06, 95% confidence interval [CI] 1.64 to 2.60, p <0.001). There was a trend toward predicting thromboembolism and atrial fibrillation (HR 1.34, 95% CI 0.96 to 1.87, p = 0.08; and HR 1.31, 95% CI 0.98 to 1.74, p = 0.07). As we have previously described, the CHA2DS2-VASc score was predictive of the 3 outcomes, where increasing risk was seen with higher scores and this was most substantial for the outcomes of death and thromboembolism.

Mortality, thromboembolism, and incident atrial fibrillation correlated significantly with increasing CHA2DS2-VASc-R score (Figure 2). The respective C-statistics mildly increased for all outcomes with the addition of renal impairment to the CHA2DS2-VASc score, although this improvement was not significant for atrial fibrillation. Specifically, the C-indexes for thromboembolism, survival, and
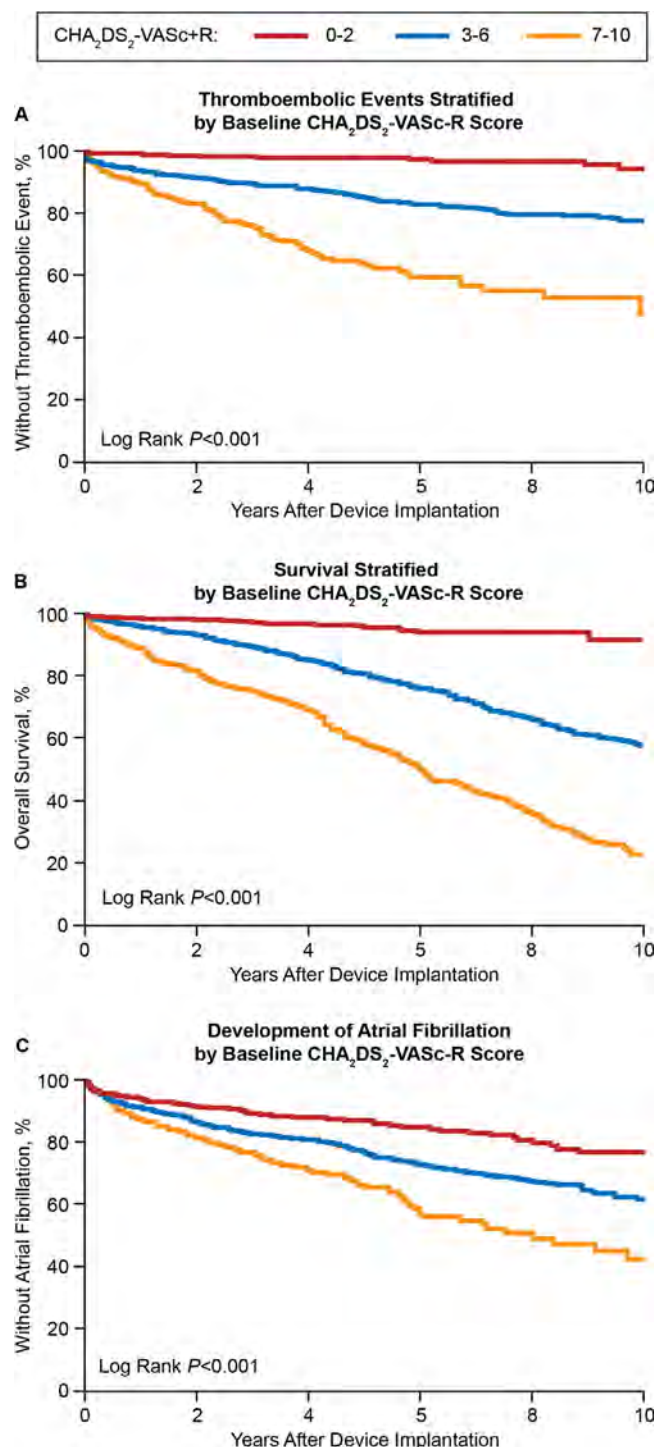
Figure 2. Study outcomes stratified by baseline CHA2DS-VASc-R scores.

atrial fibrillation increased from 0.72 to 0.73 (p = 0.006), 0.70 to 0.72 (p <0.001), and 0.606 to 0.607 (p = 0.20), respectively.

Table 3 shows the associated risk of study outcomes for CHA2DS2-VASc scores and CKD stages. CKD stages 4 and 5 were combined into 1 group given the relatively small percentage of patients in the 2 groups compared with the other CKD stages. CKD stage was associated with a

Table 2
Risk of outcomes by CHA2DS2-VASc score and renal impairment*

Outcome	Hazard ratio	95% CI		p value
Evaluated variable		Lower	Upper	
Death				
CHA2DS2-VASc 2-5	5.16	2.65	10.06	<0.0001
CHA2DS2-VASc 6-9	11.26	5.75	22.05	<0.0001
Renal impairment	2.06	1.64	2.60	<0.0001
Baseline anticoagulation	0.76	0.53	1.09	0.13
Thromboembolic events				
CHA2DS2-VASc 2-5	3.52	1.64	7.56	0.001
CHA2DS2-VASc 6-9	9.26	4.29	19.99	<0.0001
Renal impairment	1.34	0.96	1.87	0.08
Baseline anticoagulation	1.89	1.33	2.69	0.0004
Atrial fibrillation				
CHA2DS2-VASc 2-5	1.59	1.09	2.32	0.02
CHA2DS2-VASc 6-9	2.40	1.61	3.57	<0.0001
Renal impairment	1.31	0.98	1.74	0.07
Baseline anticoagulation	1.29	0.93	1.78	0.12

* CKD stage 3 or greater defined by International Classification of Diseases, Ninth Revision codes.

Table 3
Risk of outcomes by CHA2DS2-VASc score and chronic kidney disease stage*

Outcome	Hazard ratio	95% CI		p value
Evaluated variable		Lower	Upper	
Death				
CHA2DS2-VASc Score	1.35	1.27	1.43	<0.0001
Chronic kidney disease stage	1.58	1.33	1.89	<0.0001
CHA2DS2-VASc 3-6	6.55	2.42	17.68	0.0002
CHA2DS2-VASc 7-9	15.08	5.48	41.46	<0.0001
Chronic kidney disease 2	0.69	0.40	1.20	0.19
Chronic kidney disease 3	1.40	0.82	2.38	0.22
Chronic kidney disease 4-5	2.74	1.46	5.14	0.002
Thromboembolic events				
CHA2DS2-VASc score	1.38	1.28	1.49	<0.0001
Chronic kidney disease stage	1.09	0.87	1.36	0.45
CHA2DS2-VASc 3-6	3.10	1.36	7.09	0.007
CHA2DS2-VASc 7-9	9.35	3.94	22.16	<0.0001
Chronic kidney disease 2	1.82	0.79	4.18	0.16
Chronic kidney disease 3	2.23	0.97	5.14	0.06
Chronic kidney disease 4-5	1.96	0.69	5.58	0.21
Atrial fibrillation				
CHA2DS2-VASc score	1.15	1.08	1.22	<0.0001
Chronic kidney disease stage	1.15	0.95	1.38	0.15
CHA2DS2-VASc 3-6	1.56	0.98	2.49	0.06
CHA2DS2-VASc 7-9	2.60	1.52	4.42	0.001
Chronic kidney disease 2	1.62	0.88	3.02	0.12
Chronic kidney disease 3	1.88	1.01	3.51	0.048
Chronic kidney disease 4-5	1.92	0.82	4.47	0.13

* Defined by GFR data.

significantly increased risk of mortality and nonsignificant slightly increased risks of thromboembolism and incident atrial fibrillation. Although nonsignificant, HRs for thromboembolism were on the order of 2 for subject CKD stages compared with CKD stage 1. Figure 3 shows the relation between various CKD stages and the outcomes. A separate analysis was completed assuming those patients without lab data had normal renal function (Supplemental material). In this analysis (n = 1,606), CKD stage was associated with a nonsignificant nominally increased risk of mortality and thromboembolism.

Discussion

Our results show that adding a point for renal impairment to the CHA2DS2-VASc score improves prediction of thromboembolism and mortality in those without atrial fibrillation in a population with implantable cardiac devices. However, the magnitude of change in C-statistics was small. Associations between renal impairment and increased primary outcomes were significant for mortality and trending toward significance for thromboembolism and atrial fibrillation.

The risk of stroke is elevated in the setting of CKD.[12] Some previous evidence supports adding renal function to thromboembolic risk prediction schemas in those with atrial fibrillation,[8] however, this has not been evaluated in populations without atrial fibrillation. The CHA2DS2-VASc score is commonly employed to risk-stratify patients with atrial fibrillation for anticoagulation to prevent stroke. Our

recent study found that the CHA2DS2-VASc score remained predictive of thromboembolic events and mortality in a population without atrial fibrillation with implantable cardiac devices.[4] Studies in populations with previous stroke have also found that the CHA2DS2-VASc score was predictive of short- and long-term stroke outcomes in patients without atrial fibrillation.[13-15] Increasing evidence supports a relation among stroke and atrial inflammation, fibrosis, and filling pressure.[16-18] Atrial fibrosis and inflammation may contribute to both the pathophysiology of atrial fibrillation and thromboembolism and perhaps explain the lack of temporal relation between stroke events and paroxysms of atrial fibrillation or atrial tachyarrhythmias detected by implantable cardiac devices.[19,20]

Our findings in a population without atrial fibrillation further question a causal relation between atrial fibrillation and stroke. The ASSERT and IMPACT studies, which did not show that atrial tachyarrhythmias precede embolic events, also weaken the case for causality. Specifically, only 8% of patients in the ASSERT study had subclinical atrial fibrillation within the 30 days preceding thromboembolic events,[21] and only 29% of thromboembolic events followed atrial tachyarrhythmias in the IMPACT study.[22] Furthermore, the risk of stroke remains elevated in patients with atrial fibrillation even after sinus rhythm is maintained.[23] Successful ablation of atrial fibrillation does not cease progression of atrial fibrosis.[24] Fibrotic atrial cardiomyopathy may explain the aforementioned observations.[25] We are increasingly recognizing the importance of atrial fibrosis as it pertains to stroke.[18] The CHADS2 and CHA2DS2-VASc scores have been shown to correlate with atrial fibrosis and inflammatory markers in patients with atrial fibrillation.[26,27] Perhaps with further research, the clinical focus will be less on documenting atrial fibrillation before initiating anticoagulation, and more on conducting a comprehensive risk assessment for stroke including markers of atrial fibrosis in addition to clinical variables. The addition of renal impairment to thromboembolism prediction tools may provide greater value in populations without atrial fibrillation when making this assessment given the absence of atrial fibrillation as a strong risk factor.

Our results support further study whether those without atrial fibrillation and particularly high CHA2DS2-VASc-R scores might benefit from some degree of anticoagulation. Others have questioned whether patients without atrial fibrillation at high risk of stroke would benefit from anticoagulation citing atrial fibrotic cardiomyopathy as a possible underlying progressive cause of stroke and a future therapeutic target.[28] More liberal prescribing of anticoagulation may be seen in the future, particularly given the greater efficacy and lower risk of bleeding seen with newer oral agents.[29] We feel that larger, prospective studies are needed to further evaluate our findings and the effect of anticoagulation on incident thromboembolism before recommending the CHA2DS2-VASc-R score to risk stratify patients without atrial fibrillation for anticoagulation.

Limitations of the study include that it is retrospective. The population had implantable cardiac devices and a high degree of co-morbidity, which limits generalization of the results. ICD-9 diagnosis codes were used to define outcomes, atrial fibrillation, renal impairment, and CHA2DS2-
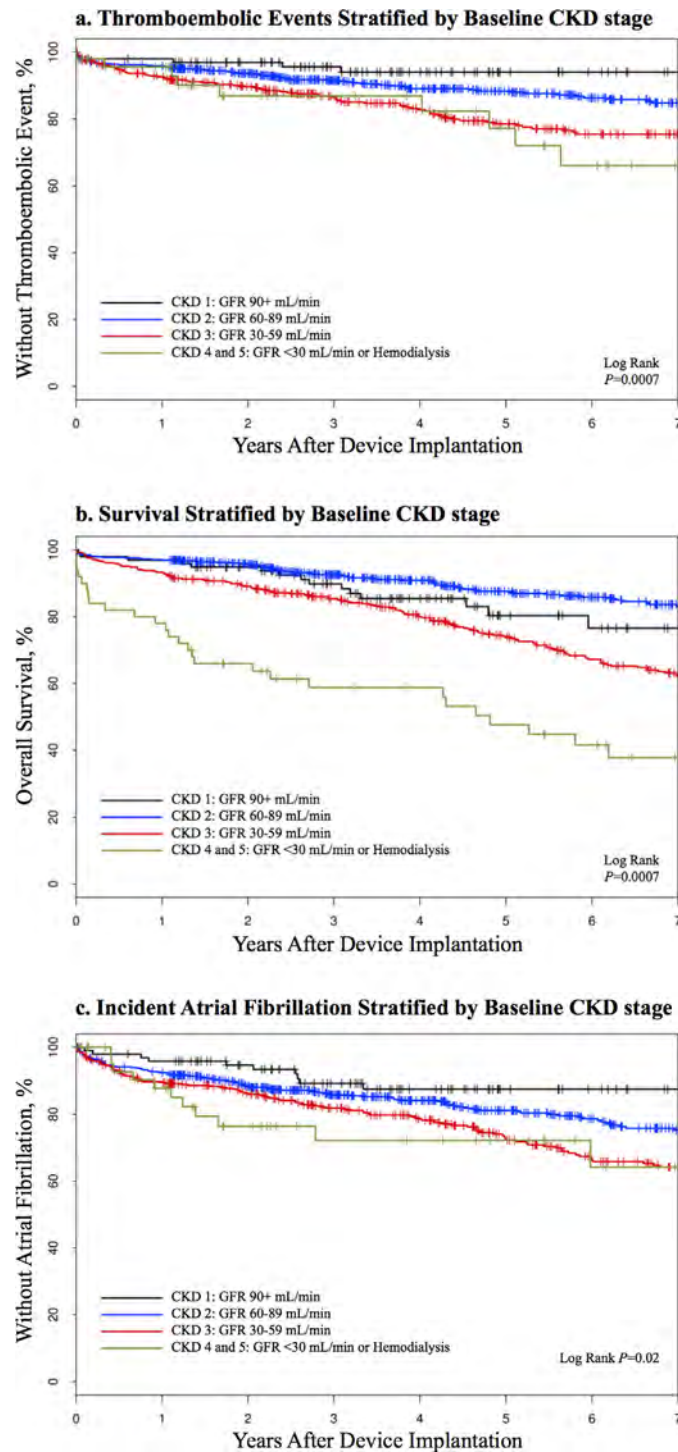
Figure 3. Study outcomes stratified by baseline CKD stage. CKD = chronic kidney disease, GFR = glomerular filtration rate.

VASc components. Cardiac device data were not manually interrogated; therefore, the assessment regarding some fraction of patients as either not having or developing atrial fibrillation may be inaccurate. Specifically, atrial fibrillation in the population may be over or underrepresented depending on the device settings. The size of the population with renal impairment was relatively small (n = 207 patients

[13%]) compared with the total population evaluated, which may account for the nonsignificant improvement in prediction for thromboembolism and atrial fibrillation. A minority of the population received oral anticoagulation (8% at baseline and 14% during the study period).

The present study shows that adding a point for renal impairment to the CHA2DS2-VASc score significantly

improved prediction of thromboembolism and mortality in a population with implantable cardiac devices without atrial fibrillation, although the magnitude of improvement was small. Development of atrial fibrillation correlated with increasing CHA2DS2-VASc-R score. Our findings warrant further research to establish if some degree of anticoagulation is of benefit in patients without atrial fibrillation and high CHA2DS2-VASc-R scores.

Disclosures

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

Authorship

All investigators listed have contributed sufficiently to the project to be included as investigators and are responsible for the study design, manuscript content and editorial decisions. All investigators reviewed and approved the final version.

Supplementary Data

Supplementary data associated with this article can be found, in the online version https://doi.org/10.1016/j.amjcard.2018.04.049.

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