Evaluation Of Two Thromboembolism (TE) Risk Methods And Oral Anticoagulation Use Among Cardiac Device Patients With Atrial Tachyarrhythmias (AT)

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Abstract

Background: In the implantable cardiac device (CD) population, not only can clinically silent atrial tachyarrythmias (AT) be detected, but an associated AT burden can be documented. There are two methods of determining stroke risk: $CHADS_2$ and CHA_2DS_2-VASc. Recommendations for initiating anticoagulation based on stroke risk profiles and/or AT burden remain unclear for device-detected AT.

Objective: Aims of this study were to reveal the AT burden among CD patients, determine $CHADS_2$ and CHA_2DS_2-VASc scores among patients with an AT burden, and evaluate current practices for anticoagulation.

Methods: Records were reviewed from patients undergoing a new CD implant within the last three years from two device clinics. Continuous variables were expressed as mean with standard deviation (SD) and categorical variables were stated as numbers and percentages. The categorical variables were compared using the Chi2 Square test and the continuous variables were compared using the independent 2-sided t-test.

Results: There were 275 CD patients enrolled. Eighty-seven had an AT burden and 188 patients did not have an AT burden. CD patients with AT burden were older than those without AT burden [69 (11), p=0.007]. Patients with AT burden had more hypertension and previous history of stroke (p=0.038, p=0.005) compared to those without AT burden. Both the $CHADS_2$ and CHA_2DS_2-VASc mean scores were higher in patients with an AT burden (p=0.018 and p=0.041). Thirty patients with a previous history of AT were on anticoagulation (p=<0.001) prior to implant. Forty-eight patients had a new diagnosis of AT (NDAT) and 46% (n=22) were started on anticoagulation.

Conclusions: An AT burden was detected in 32% of patients with at least 75% falling within a high-risk category using both scores. However, less than half of NDAT patients were started on anticoagulation. The use of oral anticoagulation in practice remains inconsistent and further randomized trials are recommended.

Introduction

Over 400,000 implantable cardiac devices (CD) are implanted each year in the U.S.[1] Clinically silent atrial tachyarrhythmias (AT), or rapid atrial rates, are detected in many of these patients in the absence of clinical evidence.[1] The introduction of implantable CD with capacity to detect, quantify, and store asymptomatic AT episodes has resulted in new insights into clinically silent AT.[2] Many

of the manufacturers define AT detection with nominal settings of atrial rate >175 beats per minute (bpm) lasting ≥ 20 seconds, but this feature is programmable. Device manufacturers quantify AT burden using various criteria, which include the following: (1) percentage of total time spent in AT, (2) number of AT episodes, (3) duration of AT episodes, (4) total time spent in AT, and lastly, (5) aggregate duration of AT episodes detected by the device on a given day. The AT burden could be composed of multiple episodes on a single day or a portion of a single episode spanning multiple days. Consistently, the manufacturers define AT burden as a percentage of total time since last cleared, number of episodes, and maximum duration of time spent in AT.

A subset study conducted by the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) investigators, clinically silent ATs were detected in one tenth of the patients three months after implantation and were detected at least once during a mean

Table 1:	Summary of hybrid (combined endocardial and epicardial) ablation studies for treatment of atrial fibrillation.				
	All Patients (N=275)	Patients with AT Burden (N=87)		Patients without AT Burden (N=188)	P-value*
		Previous dx (N=39)	New dx (N=48)		
Gender, N (%)					
Male	199 (72)	31 (79)	41 (85)	127 (68)	0.009†
Female	76 (28)	31 (79)	7 (15)	61 (32)	
Age (years), Mean (SD)	65(14)	69(11)	69(11)	64(15)	0.007‡
Type of Device, N (%)					0.703†
Pacemaker	161 (59)	27 (69)	28 (58)	106 (56)	
Defibrillator	57 (21)	7 (18)	10 (21)	40 (21)	
CRT-D[1]	56 (20)	5 (13)	10 (21)	41 (22)	
CRT-P[2]	1 (0)	0	0	1 (1)	
TE Risk, Mean (SD)					
CHADS$_2$	2.1 (1.13)	2.5$^\phi$	2.2$^\phi$	2.0 (1.09)	0.018‡
CHA$_2$DS$_2$-VASc	2.1 (1.13)	3.7$^\phi$	3.5$^\phi$	3.2 (1.42)	0.041‡
Comorbidities, N (%)					
LVEF ≤40%	103 (37)	12 (31)	17 (35)	74 (39)	0.337†
Hypertension	239 (87)	39 (100)	42 (88)	158 (84)	0.038†
Diabetes Mellitus	125 (46)	16 (41)	21 (43)	88 (46)	0.507†
Prior TIA or CVA	27 (10)	9 (23)	6 (13)	12 (6)	0.005†
Vascular Disease	121 (44)	17 (43)	22 (46)	82 (43)	0.851†
On Anticoagulation					
Prior to implant, N (%)	48 (17)	30 (77)	2 (4)	16 (85)	<0.001†

* Comparisons are for patients with and without AT burden
†. Chi-square
‡. Independent samples t-test
φ, 5% Trimmed mean
¹Cardiac resynchronization therapy with defibrillator
²Cardiac resynchronization therapy without defibrillator

follow-up period of 2.5 years in 34.7% of the patients.[1] Although asymptomatic, clinically silent ATs still have the risk of thromboembolism (TE) that symptomatic ATs have.[3,4] Studies indicate AT is found incidentally in 15-30% of patients presenting with strokes.[5,6] Similarly, one quarter of strokes are of unknown cause, and subclinical ATs may be a common etiologic factor.[1] A retrospective review of a subgroup of 312 patients from the Mode Selection Trial (MOST) demonstrated the risk of death or stroke was increased by a factor of 2.5 in patients who had at least one episode of high atrial rate detected on an implantable CD.[7] The TRENDS investigators had previously determined an episode of AT > 6 hours was associated with doubling the risk of TE.[8] In contrast, the ASSERT study demonstrated patients with high rate AT episodes > 6 minutes during an initial 3-month stratification period were at a 2.5-fold increase risk of subsequent stroke.[9] Furthermore, device-detected atrial arrhythmia burdens > 3.8 hours on a single day have also been associated with a significant increase in TE among high-risk patients with HF.[9] It is still not known whether there is a critical value of daily AT burden that has prognostic significance.[7] Further research is needed to specify the amount of AT burden in this population and the relationship to TE risk.

The Congestive Heart Failure (CHF), Hypertension, Age ≥75 years, Diabetes mellitus, Stroke known as CHADS$_2$ has become the standard assessment TE risk method currently used in clinical practice. First described in the 2006 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) guidelines; it was used to subdivide patients into three categories: those with low, intermediate, or high risk for AT-related TE.[10,11] Cohorts have indicated 30-50% of patients have a CHADS$_2$ score of 1 without a well-defined recommendation to either start aspirin or anticoagulation.[12] A recent score, incorporated into the European Society of Cardiology (ESC), has been proposed using CHF/LVEF ≤ 40, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke (CHADS$_2$), Vascular Disease, Age 65-74 years, Sex category (CHA$_2$DS$_2$-VASc) to further risk stratify patients that may have previously fallen within the intermediate risk category.[13] The score relies on "definitive risk factors" (age 75 and prior CVA/TIA) and "combination risk factors" (CHF, hypertension, age 65-74 years, diabetes, vascular disease, and female gender).[14] There is more clarity with the CHA$_2$DS$_2$-VASc scheme because studies indicate fewer patients fall into the intermediate group.[12]

Within the CD population, many patients with clinically silent AT may be in a higher risk category with the CHA$_2$DS$_2$-VASc schema, than the CHADS$_2$. This is because more patients have "combination and definitive risk factors" for two reasons: 1) patients with defibrillators primarily having ischemic heart disease and (2) more elderly patients will have conduction disease necessitating a pacemaker. Therefore, there are significant implications for both cost and TE risk. More research needs to be done to determine if device-detected AT should be treated with the same anticoagulation recommendations as clinical AT. The primary purpose of this study was to evaluate two methods of TE risk among CD patients with AT and assess anticoagulation use in this population. The aims of this study were to 1) evaluate the AT burden among CD patients, (2) determine CHADS$_2$ and CHAD$_2$DS$_2$-VASc scores among CD patients with an AT burden, and (3) evaluate current practices for anticoagulation.

Methodology

Setting

The study is a retrospective, comparative design involving a review of records from two CD clinics in the southwest. IRB approval was granted from the University of Texas Health Science Center at San Antonio (UTHSCSA) and University of Alabama.

Sample

The study sample included males and females, age 18 and above who had received a CD implant within the past three years. Records were reviewed manually from patients who had undergone new implantation of a CD, such as a pacemaker, defibrillator, or resynchronization device, for a sample size of 275 patients. Inclusion criteria was:

• Patient with an appropriate indication for a cardiac rhythm management implantable device, which can include bradyarrhythmias, ventricular tachyarrhythmias, ischemic and nonischemic cardiomyopathies or CHF
• Patient has been followed routinely, with at least 2 visits a year
• Patient > 18 years old
• Device has ability to store, detect, quantify AT episodes
• Exclusion Criteria will include:
• Pacemaker or resynchronization device with single ventricular lead(s) for permanent AT
• Defibrillator with a only a single high voltage lead
• Receiving the device as a replacement
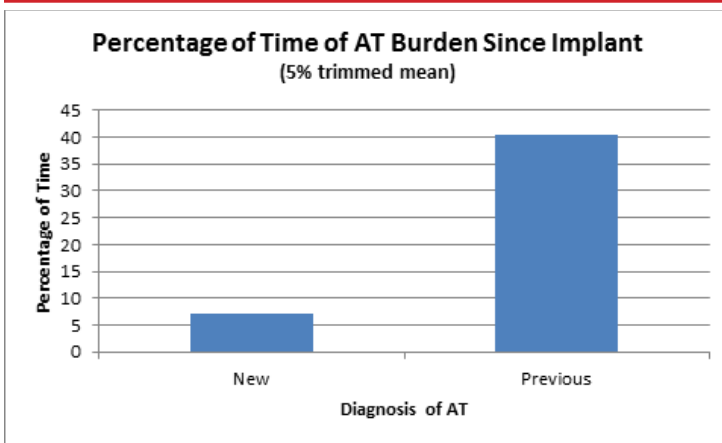
Figure 1: Mean Atrial Tachyarrhythmia (AT) Burden from Time of Implant for Patients with Previous AT and New AT

Procedures/Data collection

AIM 1: Evaluate the AT burden among CD patients

The device manufacturers provided the PI with a list of patients that have been implanted in the last 3 years. Data was obtained from existing progress notes from medical records, clinic device programmers, and interrogation reports. For the purpose of this study, episodes of AT were defined as atrial rates of at least 220 beats/min and with an onset of at least 5 minutes in duration. Multiple studies have indicated good sensitivity and specificity for AT with these parameters.[15] Once device-detected AT episode was established, data collection included if anticoagulation was initiated and the average amount of time (defined as a percentage of time) the patient is in an AT since the implant of the device.

AIM 2: Determine $CHADS_2$ and CHA_2DS_2-VASc scores among CD patients with an AT burden

For patients with any AT burden, both $CHADS_2$ and CHA_2DS_2-VASc scores were calculated. To calculate the $CHADS_2$ score patients received 1 point for each diagnosis of CHF, hypertension (blood pressure consistently over 140/90 mm Hg or being treated with anti-HTN agents), age ≥75 years, or diabetes mellitus and 2 points if they have a history of TIA or stroke. The CHA_2DS_2-VASc score was calculated by including non-major stroke risk factors of age 65-74 (1 point), female gender (1 point) and vascular disease (1 point). In the CHA_2DS_2-VASc score, 'age 75 and above' also has extra weight, with 2 points.

AIM 3: Evaluate current practices for anticoagulation

Anticoagulation status was assessed by reviewing the medication profile or progress notes for warfarin or the new oral anticoagulation (NOAC) agents in the medical record. Any patients with the diagnosis of stroke, TIA or systemic embolism since CD implant were also taken into consideration.

Data Analysis

Continuous variables were expressed as mean with standard deviation (SD) and categorical variables were stated as numbers and percentages. The categorical variables were compared using the Chi2 Square test and the continuous variables were compared using the independent 2-sided t-test for significance of differences. Five percent trimmed means tests were used for those variables with significant outliers in order to not skew results. For patients with an AT burden, the $CHADS_2$ and CHA_2DS_2-VASc scores were calculated and plotted to indicate the distribution of $CHADS_2$ and CHA_2DS_2-VASc scores among patients with a previous history of AT and new diagnosis of AT (NDAT). Graphs were drafted to indicate the number of patients where oral anticoagulation is recommended ($CHADS_2$ and CHA_2DS_2-VASc ≥ 2) for patients with previous history of AT and NDAT. The patients that were either previously on anticoagulation or initiated on oral anticoagulation are represented in the graphs. The incidence of TE was recorded, but statistical analysis was not done because of minimal events. SPSS (SPSS Inc. Released 2007, SPSS for Windows, Version 16.0. Chicago, SPSS Inc) was used to perform the statistical analysis.

Results

Demographics

Two hundred and seventy five patients met enrollment criteria. Of the 275 patients, 72% (N= 199) were men. The mean age for all patients was 65 (SD 14). Patients either had a pacemaker (N=161, 59%), ICD (N=57, 21%), or resynchronization device (N=57, 20%). Most patients had hypertension (N= 239, 87%), then diabetes (N=125, 46%), followed by vascular disease (N=121, 44%) and CHF (N=103, 39%). Twenty-seven patients (10%) had previous history or TIA or CVA. Finally, 17 % of patients (N= 48) had been on anticoagulation prior to implant.

AT Burden and TE Risk Scores among CD Patients

Of the 275 patients, 32% (N=87) of patients had an AT burden documented on their device. The average AT burden (recorded as a percentage of total time spent in AT since implant) for patients with previous history of AT was 40.5% compared with 7.2% for patients with new diagnosis of AT (Figure 1). CD patients with AT burden were older than those without AT burden [69 (11), p=0.007]. There were no differences between the groups in comorbidities with the exception of hypertension (p=.038) and prior TIA or CVA (p=.005). Both the $CHADS_2$ and CHA_2DS_2-VASc mean scores were higher in patients with an AT burden (p=0.018 and p=0.041). Demographics and comorbidities are listed in Table 1. Finally, more patients with an AT burden were on anticoagulation prior to implant, which is to be expected as many patients of these patients had a previous diagnosis of AT (p < 0.001).

Patients with AT burden were further stratified into patients having a previous diagnosis of AT (N=39, 45%) and NDAT (N=48, 55%). Both groups had hypertension more frequently (100% for previous history of AT and 88% for newly diagnosed AT) and previous history of TIA or CVA less frequently (23% for previous history of AT and 13% for new diagnosis of AT). The mean $CHADS_2$ score for all patients was 2.1 (SD 1.13) and mean CHA_2DS_2-VASc score was 3.3 (SD 1.49). The mean $CHADS_2$ and CHA_2DS_2-VASc of patients with a previous history of AT was 2.5 and 3.7 (trimmed means), respectively. Seventy-seven percent (N=30) of these patients had been on anticoagulation prior to implant (Figure 2). For patients with NDAT , the mean $CHADS_2$ and CHA_2DS_2-VASc scores were 2.2 and 3.5 respectively, and 22 (46%) of these patients had anticoagulation therapy initiated (Figure 2).

Anticoagulation recommendations based on TE risk scores

Figure 3 indicates the distribution of $CHADS_2$ and CHA_2DS_2-VASC scores in patients with previous history of AT and NDAT burden. By applying the CHA_2DS_2-VASc score, the number of intermediate-risk patients with previous history of AT decreased from 6 (15%) to 2 (5%). For patients with a NDAT , the number of low-
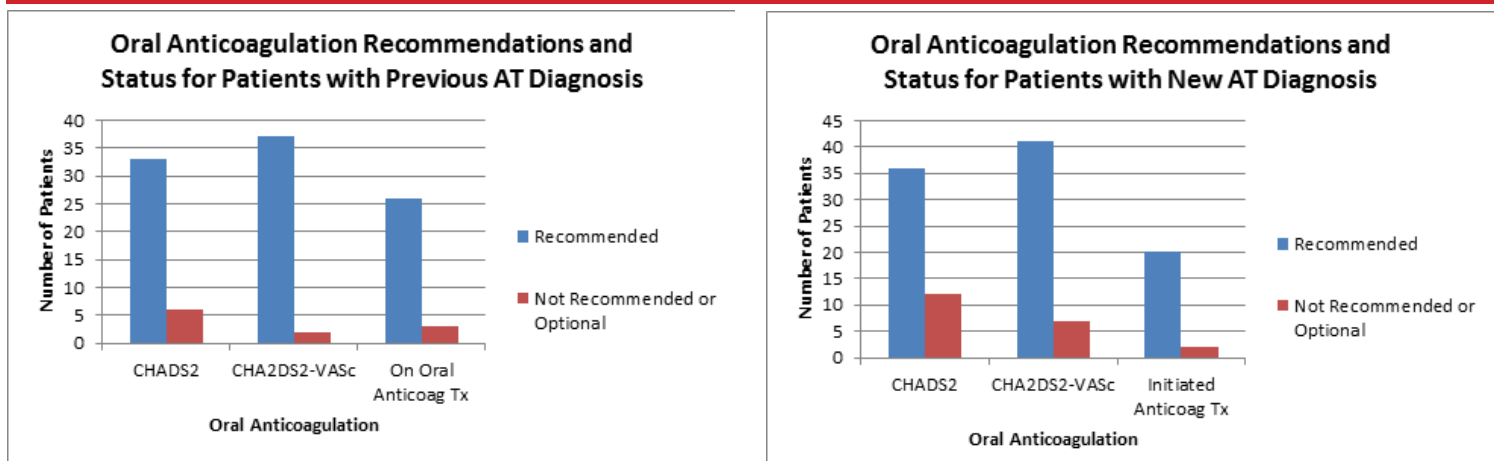
Figure 2: Anticoagulation Recommendations and Status by CHADS$_2$ and CHA$_2$DS$_2$-VASc Scores in Patients with (A) Previous Diagnosis of Atrial Tachyarrhythmias (AT) and (B) New Diagnosis of Atrial Tachyarrhythmias

risk patients (CHADS$_2$=0) decreased from 5 (10%) to 2 (4.1%) and intermediate-risk patients decreased from 7 (14.5%) to 5 (10.4%). In patients with previous diagnosis of AT, the CHADS$_2$ score classified 33 (85%) of patients requiring anticoagulation and CHA$_2$DS$_2$-VASc score classified 37 (95%) of patients requiring anticoagulation (Figure 3). For patients with NDAT, the CHADS$_2$ score classified 36 (75%) requiring anticoagulation and the CHA$_2$DS$_2$-VASc score classified 41 (85%) requiring anticoagulation. Only 22 (46%) of these patients were started on anticoagulation.

Incidence of TE events

For patients with AT burden, only 2 (2.2%) patients had documented thromboembolic events following the implant of their device. One patient was from the NDAT group and was not on oral anticoagulation at the time of the event. The patient was subsequently started on anticoagulation at the device follow-up appointment. The other patient had a previous diagnosis of AT and was on oral anticoagulation, but was subtherapeutic at the time of the event.

Discussion

The first aim was to evaluate the prevalence of AT among CD patients. In this study, 32% of patients enrolled had an AT burden, with 17% of patients had newly diagnosed AT detected on their CD. This is similar to what was reported in a study by Healey[1] where 10% of patients had AT detected at 3 months after implantation and 34% had AT detected at 2.5 years from implant. Another finding in this study is patients with a previous history of AT have a higher burden of AT, compared to patients newly diagnosed with AT. The BEATS study confirmed a higher incidence of AT after CD implantation with a previous history of AT, which is in line with the current understanding of the pathophysiology of AT as a progressive disease.[2,16] The TRENDS study had previously reported the risk of TE doubles when the arrhythmia burden exceeds 5.5 hours on a given day.[8] An increasing body of evidence has linked device-detected AT burden with an increased risk of stroke, but there still seems to be no "safe" amount of AT identified.[17] Even though CDs can yield valuable diagnostic data to guide anticoagulation therapy, providers should also evaluate patient-specific risk factors for AT-associated TE events.

The second aim of the study was to determine CHADS$_2$ and CHA$_2$DS$_2$-VASc scores among cardiac device patients with an AT burden. The mean CHADS$_2$ score for all patients was 2.1 (SD 1.13) and mean CHA$_2$DS$_2$-VASc score was 3.3 (SD 1.49). One study investigating the two risk TE scores of 1664 patients at an atrial fibrillation center indicated patients had mean CHADS$_2$ and CHA$_2$DS$_2$-VASc scores of 1.1 (1.1) and 1.8 (1.5).[14] Therefore, this suggests CD patients may have more risk factors compared to the general population. In this study, the mean CHADS$_2$ and CHA$_2$DS$_2$-VASc was significantly higher in patients with an AT burden compared to those without an AT burden, indicating there are more risk factors for stroke in the AT burden population. Patients with an AT burden were older, had more hypertension, and previous history of stroke compared to those without AT burden. Within the AT burden subset, the mean CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were higher in patients with a previous history of AT, suggesting the presence of additional risk factors can affect the overall incidence and severity of AT progression.

The detection of AT in the CD population can trigger decisions regarding initiating anticoagulation therapy. In the patients with previous history of AT, anticoagulation was recommended for 85% of patients using the CHADS$_2$ score and 95% of patients using the CHA$_2$DS$_2$-VASc score. In this subset, 30 patients (77%) were on anticoagulation. In patients with NDAT, the CHADS$_2$ score classified 36 (75%) requiring anticoagulation and the CHA$_2$DS$_2$-VASc score classified 41 (85%) requiring anticoagulation. Surprisingly, only 22 (46%) of these patients were started on anticoagulation. This number may be low because of fall risk, potential for bleeding complications, or having a low burden of AT captured on the device as the burden of AT was significantly lower in the NDAT group. These findings are comparable to a study done by Healey[18] where the use of anticoagulation was more frequent among patients with a previous history of AT (58.9%) than those with a NDAT (23.7%). The TRENDS study indicated the annual TE risk for patients with a high AT burden was 2.4%.[13] In this study, only 2 patients had TE events following their implant. A low incidence of TE limits the potential benefit of anticoagulation and emphasizes the need to better determine TE risk when considering anticoagulation therapy. Therefore, when AT burden is used in conjunction with TE risk scores, the need for anticoagulation can be determined. However, a randomized controlled trial evaluating oral anticoagulation use in device-detected AT should be done before anticoagulation is widely recommended.
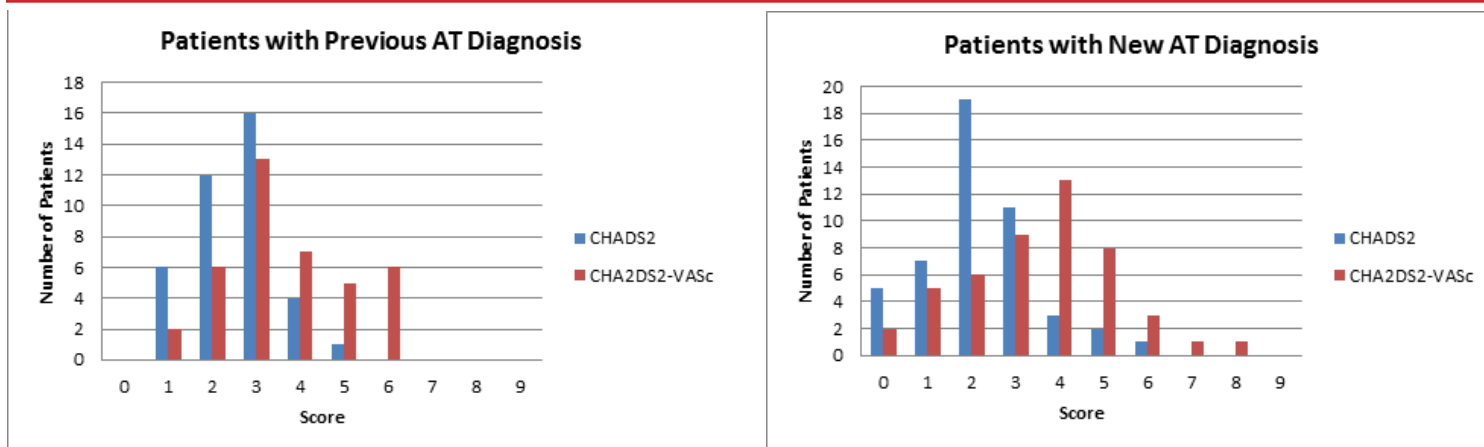
Figure 3: The Distribution of CHADS$_2$ and CHA$_2$DS$_2$-VASc Scores Among Device Patients with (A) Previous Diagnosis of Atrial Tachyarrythmias and (B) New Diagnosis of Atrial Tachyarrhythmias

Limitations

There may be sensing issues with the CD and AT burden, which can be either over or understated. Also, patients' CHADS$_2$ and CHA$_2$DS$_2$-VASc scores may change throughout the record review based on age or new comorbidities, but for the purpose of the study, only pre-implant scores were used. The majority of the sample was men and may not give and an adequate representation of the impact of CHA$_2$DS$_2$-VASc scores on gender differences among the CD population. Finally, due to the limited number of TE events, a comparison was not done between the stroke risk profiles.

Further research with a prospective study using groups randomized into each TE risk scoring scheme for anticoagulation therapy and evaluating the incidence of TE events may be helpful for the CD population. Further investigating if there is a significance of differences with the type of device (ICD, pacemaker, or CRT) with AT burden and TE risk scores may yield noteworthy data which can be applied to clinical practice. Finally, as previously mentioned, randomized trials of anticoagulation in patients with device-detected AT should be done before oral anticoagulation is widely accepted for this population.

Conclusion

This was the first study to compare two TE risk methods and evaluate current anticoagulation practice in CD patients. This study demonstrated patients with implantable cardiac devices are a high-risk population for TE events using both risk-stratification scores. However, there is still inconsistency with anticoagulation practices for this population. Over 75% of patients with clinically diagnosed AT prior to CD implant were on anticoagulation. In contrast, less than 50% of patients with newly device-detected AT were started on anticoagulation. Even though the TRENDS and ASSERT studies have previously indicated a 2-3 times risk of TE[8,9] for device-detected AT, oral anticoagulation use for this population is not widely accepted. Until more randomized trials for oral anticoagulation are conducted for this population, clinicians should still evaluate patient-specific risk factors and the amount of AT burden to trigger the decision for initiating oral anticoagulation.

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