# The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk

# The TRENDS Study

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*Background*—It is unknown if brief episodes of device-detected atrial fibrillation (AF) increase thromboembolic event (TE) risk.

- *Methods and Results*—TRENDS was a prospective, observational study enrolling patients with  $\geq 1$  stroke risk factor (heart failure, hypertension, age  $\geq 65$  years, diabetes, or prior TE) receiving pacemakers or defibrillators that monitor atrial tachycardia (AT)/AF burden (defined as the longest total AT/AF duration on any given day during the prior 30-day period). This time-varying exposure was updated daily during follow-up and related to TE risk. Annualized TE rates were determined according to AT/AF burden subsets: zero, low (<5.5 hours [median duration of subsets with nonzero burden]), and high ( $\geq 5.5$  hours). A multivariate Cox model provided hazard ratios including terms for stroke risk factors and time-varying AT/AF burden and antithrombotic therapy. Patients (n=2486) had at least 30 days of device data for analysis. During a mean follow-up of 1.4 years, annualized TE risk (including transient ischemic attacks) was 1.1% for zero, 1.1% for low, and 2.4% for high burden subsets of 30-day windows. Compared with zero burden, adjusted hazard ratios (95% CIs) in the low and high burden subsets were 0.98 (0.34 to 2.82, P=0.97) and 2.20 (0.96 to 5.05, P=0.06), respectively.
- *Conclusions*—The TE rate was low compared with patients with traditional AF with similar risk profiles. The data suggest that TE risk is a quantitative function of AT/AF burden. AT/AF burden ≥5.5 hours on any of 30 prior days appeared to double TE risk. Additional studies are needed to more precisely investigate the relationship between stroke risk and AT/AF burden. (*Circ Arrhythmia Electrophysiol.* 2009;2:474-480.)

Key Words: atrial fibrillation ■ tachyarrhythmias ■ stroke ■ risk factors ■ pacemakers

A trial fibrillation (AF) is the most commonly treated tachyarrhythmia worldwide.<sup>1</sup> Population projections indicate that the prevalence of AF could exceed 12 million by 2050 in the United States alone.<sup>2</sup> AF raises the risk of stroke 3- to 5-fold.<sup>3</sup> Chronic anticoagulation with vitamin K antagonists is effective at reducing the risk of stroke but is burdensome.<sup>4</sup>

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The stroke risk conferred by paroxysmal AF (PAF) has not been well characterized but has been arguably said to be the same as continuous AF.<sup>5–7</sup> Identification of short episodes of PAF, even in the absence of symptoms, therefore may be important to permit early intervention. Today, comprehensive detection of PAF is facilitated by pacemakers, implantable cardioverter-defibrillators (ICDs), and other implantable monitors. The incidental finding of AF events recorded by dual-chamber pacemakers and ICDs is extremely common and poses a clinical challenge because their practical significance is unknown. The thromboembolic event (TE) risk attributable to these device-detected episodes of PAF remains unknown. In particular, it is not known whether there is a critical value of daily AF burden that has prognostic significance.

The purpose, therefore, of the TRENDS study was to evaluate the relationship between long-term device-detected atrial tachycardia (AT)/AF burden and TE among patients with stroke risk factors who were already scheduled for pacemaker, ICD, or cardiac resynchronization therapy (CRT) device implantation for a class I/II clinical indication. As such, the TRENDS study is not a study of patients with AF

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This study is registered at clinicaltrials.gov (NCT00279981).

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per se but a study of patients receiving such a device, some of whom have a history of AF. It has previously been shown that the sensitivity and specificity for AF detection using implanted devices with settings similar to those used in the present study is very high.<sup>8</sup> We hypothesized that more AT/AF burden would be independently associated with increased stroke risk after adjusting for anticoagulation treatment and risk factors.

# Methods

# **Study Population**

The original TRENDS study design has been described previously.<sup>9</sup> Briefly, TRENDS was a prospective, observational cohort study designed to assess the relationship between the risk of TE and AT/AF burden detected by devices capable of continuous heart rhythm monitoring. Consenting patients were included if they had (1) an established class I/II indication for an implantable cardiac rhythm device that was capable of long-term monitoring of AT/AF burden and (2) 1 or more stroke risk factors based on 2001 guidelines in effect at the time this study began (including history of congestive heart failure or hypertension, age  $\geq$ 65 years, diabetes mellitus, or prior stroke/transient ischemic attack [TIA]).<sup>10,11</sup> Exclusion criteria were (1) replacement devices, (2) long-standing persistent AF, (3) known reentrant supraventricular tachycardias, (4) terminal illness limiting survival, (5) unable or unwilling to consent, and (6) concurrently enrolled in a conflicting drug or device study.

Patients both with and without a history of AF were enrolled. Patients with no history of AF and no new AT/AF detected by the device within the first year of follow-up were censored after 1 year as part of the original analysis plan. We continued to follow patients who had a history of AF and patients without a history of AF who had new device-detected AT/AF during the first year of follow-up.

#### Follow-Up

Patients were followed at 3-month intervals, at which time device diagnostic information was collected. Clinical evaluations, including screening for potential outcome events, were completed every 6 months. A standardized stroke symptom questionnaire was administered at each patient contact to assist in identifying potential TEs. The use of antithrombotic therapy was determined by the patients' physicians and recorded at each follow-up visit. INR values were not comprehensively collected. Physicians were encouraged to follow published guidelines for use of antithrombotic therapy.<sup>11</sup> The first patient was enrolled on November 6, 2003, and study follow-up ended on June 28, 2007. The study was terminated earlier than planned because the observed event rate was too low to achieve the primary study aim by the planned termination date (see Analysis Plan, below).

# **Device Programming**

Devices (Medronic, Minneapolis, Minn) were programmed to dualchamber operation with active mode switching. AT/AF detection was programmed to the nominal settings (atrial rate >175 bpm lasting  $\geq$ 20 seconds) to ensure consistent device programming at all centers. Prior studies using similar detection algorithms have shown **Figure 1.** Example of long-term continuous recording of AT/AF burden data from an implantable device. Each black vertical line represents the total hours of AT/AF on each day.

>95% sensitivity and specificity for detection of AT/AF episodes and measurement of AT/AF burden.<sup>12</sup> There was no attempt in this study to distinguish between atrial tachycardias, atrial flutter, or AF because our goal was to study the easily accessible and readily available stored diagnostic data from the device memory that is available on initial interrogation of the device, as seen in Figure 1. Stored intracardiac electrograms were not available for each episode because of device memory limitations. AT/AF burden was measured in hours per day and was tabulated daily by the device (Figure 1).

The study protocol was approved by the institutional review board of each participating center, and all patients gave informed consent.

#### **Primary Outcome Events**

Study outcome events (TEs) consisted of ischemic stroke, TIA, and systemic embolism. Ischemic stroke was defined as the abrupt onset of a focal neurological deficit consistent with a focal cerebrovascular disruption of flow persisting for more than 24 hours and not explained by another disease process (eg, abscess, tumor). TIA was similarly defined as a focal neurological deficit lasting less than 24 hours and believed to be due to cerebral ischemia. Nonstroke systemic embolism was a clinical event consistent with an arterial occlusion, in the absence of significant atherosclerosis of the affected artery, excluding pulmonary embolism and myocardial infarction. Primary hemorrhagic strokes were documented but were not considered a TE. The medical records of all patients with possible outcome events were adjudicated by a committee of 3 neurologists who were blinded to the AT/AF burden data.

# **Analysis Plan**

The goal of the original analysis plan was to determine the relationship between median daily AT/AF burden and TEs in patients not treated with warfarin who had a history of AF and/or had device documented AT/AF in the first year.<sup>9</sup> Patients started on warfarin were to be censored at the time of warfarin initiation. Of the 2813 patients followed, 1563 were excluded from the original primary study group because they had no history of AF and no new AT/AF detected by 1 year. An additional 432 patients were excluded from the primary study group because of warfarin use at baseline. This left 818 patients in the primary study group. Only 14 patients in this group had a TE during follow-up (8 ischemic strokes, 5 TIA, and 1 systemic embolus), for a rate too low (1.3% per year) for a statistically meaningful analysis.

A secondary analysis of the overall study group is the focus of the current report. This secondary analysis was devised considering only the overall TE rate in the primary study group and before assessing the relationship between AT/AF burden and TE risk. In this secondary analysis, we included patients who were anticoagulated and patients who did not have AT/AF; the latter is a logical control group for those with AT/AF. The overall study group included all enrolled patients, regardless of anticoagulation and/or aspirin therapy, and regardless of AF history or occurrence of AT/AF (defined as an episode of AT/AF  $\geq$ 20 seconds) during follow-up, provided there was a minimum of 30 days of analyzable device data. Of the 2813 patients followed, 327 were excluded from the analysis because they did not have at least 30 days with device data available. The analyzable overall study group, therefore, consisted of the remaining 2486 patients (Figure 2).



Figure 2. Assembly of the cohort.

AT/AF burden was defined as the maximum number of hours of AT/AF on any day during the antecedent 30 days and may have included more than 1 episode of AT/AF on that day. Thirty-day windows were selected to maintain a balance between too short of a time frame (in which the likelihood of observing any AT/AF is low) and too long of a time frame (in which observed AT/AF may not be temporally related to a TE). Daily AT/AF burden was selected based on the capability of the devices to monitor continuously and store AT/AF burden data each day over prolonged periods of time (Figure 1). As an alternate analysis, we also examined the total cumulative time spent in AT/AF over each 30-day window. AT/AF burden was a time-varying exposure updated daily resulting in sequential overlapping 30-day "rolling windows" for each patient (ie, the first window consisted of days 1 to 30, the second window consisted of days 2 to 31, and so on; Figure 3). This approach was dictated by the fact that episodes of AT/AF were assessed on a daily basis, but AT/AF burden was defined as a 30-day exposure. Examples of similar analytic strategies in the medical literature are available.<sup>13</sup>

AT/AF burden was divided into 3 subsets: 30-day windows with zero AT/AF burden, 30-day windows with low AT/AF burden, and 30-day windows with high AT/AF burden. Because we had no pathophysiologic basis for defining a threshold for high AT/AF burden, we used the observed median value of AT/AF burden, among those with nonzero burden, as the cutoff between low and high AT/AF burden. Such a dichotomization would lead to increased statistical power. This cutoff was defined before data analysis. Time-varying AT/AF burden (categorized as zero, low, and high) was then related to the TE hazard ratio in the Cox regression model.

### **Statistics**

Continuous variables are presented as means and categorical variables as percentages. The categorical variables were compared using  $\chi^2$  test and the continuous variables were compared using a 2-sample *t* test. The probability values were not adjusted for multiple comparisons. Baseline age among the pacemaker, ICD, and CRT groups were compared using a 1-way ANOVA model. For the calculation of

the event rate among all 2813 followed patients, follow-up began at implantation and continued through all available clinical follow-up. For patients who had TEs during the follow-up, their follow-up ended at the time of the TE. For the analyses of rates and hazards according to AT/AF burden, the follow-up ended with the last available assessment date of AT/AF burden by the device. Patients were also censored at the date of sustaining an outcome event, death, device explant without replacement, withdrawal of consent, and last follow-up date for those lost to follow-up. Windows with zero, low, and high AT/AF burden were summed to provide denominators for event rates. Annualized TE rates with 95% CIs were calculated with and without inclusion of TIAs using generalized estimating equations. The time-varying AT/AF burden (categorized as zero, low, and high) was then related to the TE hazard ratio in a Cox regression model, which included baseline stroke risk factors and timedependent use of warfarin and aspirin. A significance level of 0.05 was used, and all statistical analyses were performed using SAS 9.1.3 Service Pack 4 Windows version.

# Results

# **Study Population**

There were 3045 patients enrolled from 116 clinical sites in the United States, Canada, and Australia. After excluding those patients who were implanted with a nonstudy device or did not have an informed consent, 2813 patients remained and were followed (Figure 2). The overall mean age was 71 years and varied according to the type of device received: 75.5 years for pacemaker, 65.9 years for ICD, and 68.3 years for CRT (P<0.001). The overall mean CHADS<sub>2</sub> score (congestive heart failure, hypertension, age, diabetes, prior stroke/ TIA) was 2.2±1.2, reflecting a moderately high expected stroke risk.



**Figure 3.** Example of 30-day windows assessing AT/AF burden from data collected from device diagnostics. AT/AF burden is the maximum duration of AT/AF on any given day in the preceding 30 days. AT/AF burden was a time-varying exposure in our analyses and was updated daily. Gray shaded areas correspond to 3 representative 30-day windows with zero, low (<5.5 hours on all days), and high ( $\geq$ 5.5 hours on at least 1 day) AT/AF burden, respectively.

Variable	Overall Study Group (n=2486)	Documented AF at Time of Enrollment or New Diagnosis of AT/AF ( $\geq$ 20 s) After Study Enrollment (n=1389)	No Prior AF and No New AT/AF After Study Enrollment (n=1097)	P Value Between AT/AF and No AT/AF Groups
Age, y	70.9±11.1	71.7±11.0	70.0±11.1	0.0003
Male sex	1650 (66.4)	925 (66.6)	725 (66.1)	0.79
Device type				
Pacemaker	1234 (49.6)	721 (51.9)	513 (46.8)	0.03
ICD	781 (31.4)	409 (29.5)	372 (33.9)	
CRT	471 (19.0)	259 (18.7)	212 (19.3)	
CHADS <sub>2</sub> score	2.2±1.2	2.2±1.2	2.2±1.2	0.34
0–1	713 (28.7)	393 (28.3)	320 (29.2)	0.83
2	863 (34.7)	481 (34.6)	382 (34.8)	
3–5	910 (36.6)	515 (37.1)	395 (36.0)	
History of				
Congestive heart failure	1479 (59.5)	843 (60.7)	636 (58.0)	0.17
Hypertension	1887 (75.9)	1065 (76.7)	822 (74.9)	0.31
Diabetes mellitus	783 (31.5)	393 (28.3)	390 (35.6)	0.0001
Prior thromboembolic event	333 (13.4)	190 (13.7)	143 (13.0)	0.68
Hemorrhagic stroke	31 (1.2)	15 (1.1)	16 (1.5)	0.51
Systolic blood pressure, mm Hg	133.3±22.5*	133.2±22.2†	134.4±22.8‡	0.79
Diastolic blood pressure, mm Hg	70.6±12.1*	71.2±12.1†	69.6±12.1‡	0.007
Coronary artery disease	1577 (63.4)	859 (61.8)	718 (65.5)	0.06
Previously documented AF	498 (20.0)	498 (35.9)	0 (0)	< 0.0001
Drug prescribed at baseline				
Warfarin	517 (20.8)	407 (29.3)	110 (10.0)	< 0.0001
Aspirin	1547 (62.2)	824 (59.3)	723 (65.9)	0.0008
Class I and III antiarrhythmic drug	245 (9.9)	192 (13.8)	53 (4.8)	< 0.0001
Other antiplatelet	559 (22.5)	280 (20.2)	279 (25.4)	0.002

Table 1. Dascine characteristics of the overall study droup stratified by Diagnosis of P
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Data are presented as mean  $\pm$  SD or n (%).

\*n=2469; †n=1381; ‡n=1088.

After exclusion of those without a minimum of 30 days of AT/AF data, 2486 patients remained (Figure 2) (Table 1). Among these patients, those with a history of AF at the time of study enrollment or with new AT/AF detected by the device were older, were less likely to have diabetes, and had higher diastolic blood pressure measurements. Only a fifth of patients were taking warfarin at enrollment, but anticoagulation was more likely among those with a history of AF. In contrast, such patients were less likely to be taking aspirin. Antiarrhythmic medication use was uncommon but more likely among those with documented AT/AF. Within the overall study group, 135 of the 2486 patients died during follow-up.

# **AT/AF Burden**

Each 30-day window was categorized as having zero AT/AF burden, low AT/AF burden (less than median value for windows with any episodes of AT/AF), or high AT/AF burden (equal to or greater than median value for windows with any episodes of AT/AF). Fifty-three percent of study patients had no AT/AF observed at any time during follow-up, and 76% of study windows had zero AT/AF burden (Figure 4). Twenty-four percent of study windows had at least

1 episode of AT/AF. We defined AT/AF burden as the maximum daily duration of AT/AF on any given day during the preceding 30-day window. Our observed median value for AT/AF burden among 30-day windows with AT/AF was 5.5 hours.

# **Thromboembolic Events**

The average follow-up was 1.4 years (range, 0.1 to 3.3 years), with a total patient exposure of 3382 patient-years. There were 40 patients who had TEs and device data available for the 30-day window immediately preceding the TE. These 40 TEs included 20 ischemic strokes, 17 TIAs, and 3 systemic emboli, resulting in an annualized event rate (95% CI, 1.2% [0.8, 1.6%]) in the overall study group (Figure 2). Four additional TEs occurred in patients who did not have AT/AF burden data available for the 30 days immediately before the event. In addition, 7 TEs occurred among the 327 patients who were excluded from the overall study group because they did not have any 30-day period of device data. Therefore, there were a total of 51 patients with TEs (29 ischemic strokes, 19 TIAs, 3 systemic emboli), for an annualized event rate (95% CI, of 1.3% [0.9, 1.6%]) among all followed patients. Among these 51 patients with TEs, 10 had AT/AF



**Figure 4.** Distribution of AT/AF burden in all 30-day windows during study follow-up.

and were taking warfarin, 17 had AT/AF and were not taking warfarin, and 24 did not have any AT/AF between enrollment and the time of TE. The overall TE rate is similar when including all TE events (1.3%) among all followed patients or just those who have 30 days of device data available (1.2%) in the overall study group. In addition, there were 6 hemorrhagic strokes reported in the overall study population that were not considered TEs.

# **TE Rates According to AT/AF Burden**

The annualized TE rate was 1.1% for both the subset of windows with zero AT/AF burden and the subset of windows with low AT/AF burden. For windows with high AT/AF burden, the TE rate was 2.4% (Table 2). Excluding TIAs, the annualized stroke/systemic embolus rates were 0.5% for the windows with zero AT/AF burden, 1.1% for those with low AT/AF burden, and 1.8% among those with high AT/AF burden (Table 2).

After adjusting for stroke risk factors (history of ischemic stroke/TIA/nonstroke systemic embolus, history of diabetes, history of hypertension, history of congestive heart failure, and age at baseline) and time-dependent antithrombotic treatment (aspirin and warfarin use), the hazard ratio for the low AT/AF burden subset compared with the zero AT/AF burden subset was 0.98 (95% CI, 0.34 to 2.82; P=0.97). The hazard ratio for the high AT/AF burden subset compared with the zero AT/AF burden subset was 2.20 (95% CI, 0.96 to 5.05; P=0.06) (Table 3). In this analysis, use of aspirin or warfarin was not a significant determinant of outcome, but the CIs bounding our estimates were wide (hazard ratios, 1.68 [95% CI, 0.81, 3.47] for aspirin and 0.87 [95% CI, 0.41 to 1.87] for warfarin).

Table 2.	TE Rates fo	r the Overall	Study Group	(Unadjusted)
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		Annualized TE Rate
AT/AF Burden	Annualized TE Rate	Excluding TIAs
Subset	(95% CI), %	(95% CI), %
Zero AT/AF burden	1.1 (0.8–1.6)	0.5 (0.3–0.9)
Low AT/AF burden ( $<$ 5.5 h)	1.1 (0.4–2.8)	1.1 (0.4–2.8)
High AT/AF burden (5.5 h)	2.4 (1.2-4.5)	1.8 (0.9–3.8)

In the alternate analysis, we also characterized AT/AF as the total cumulative hours of AT/AF over the prior 30 days. The median value for this measure of AT/AF for those who had any AT/AF was 10.8 hours. After adjusting for stroke risk factors (history of ischemic stroke/TIA/nonstroke systemic embolus, history of diabetes, history of hypertension, history of congestive heart failure, and age at baseline) and time-dependent aspirin and warfarin use, the hazard ratio for the low AT/AF subset (<10.8 hours) compared with the zero AT/AF subset was 0.97 (95% CI, 0.34 to 2.80; P=0.96). The hazard ratio for the high AT/AF subset ( $\geq 10.8$  hours) compared with the zero AT/AF subset was 2.22 (95% CI, 0.96 to 5.10; P=0.06). These results are nearly identical to those in which AT/AF was characterized by the maximum daily duration during the antecedent 30 days (see above), reflecting the fact that the 2 measures of AT/AF burden are highly correlated. Indeed, categorization of 30-day window AT/AF burden (ie, zero, low, high) according to maximum burden on any given day was 98% identical to categorization according to cumulative duration of AT/AF.

# Discussion

The TRENDS study was designed to assess the relationship between low levels of paroxysmal AF and risk of stroke. Analyses from older randomized trials indicate that patients with "intermittent" AF have rates of stroke comparable to

Table 3.	Hazard Ratios for Thromboembolic Events Associated
With AT/A	F Burden Adjusted for Stroke Risk Factors and
Antithrom	botic Therapy

Category	Variable	Hazard Ratio (95% Cl)*	P Value
AT/AF burden	Low burden vs zero burden	0.98 (0.34, 2.82)	0.97
	High burden vs zero burden	2.20 (0.96, 5.05)	0.06

High and low burden are separated by the median value of 30-day windows having nonzero AT/AF burden; that is, high corresponds to a burden of  $\geq\!5.5$  hours, low corresponds to a burden of 20 seconds to  $<\!5.5$  hours.

\*Estimates based on Cox model with time-varying AT/AF burden and antithrombotic therapy.

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patients with persistent AF, after controlling for stroke risk factors.<sup>5,14</sup> However, patients categorized as "intermittent" AF or "paroxysmal" AF in previous trials were likely to have relatively high AF burden (high enough to be seen and documented on a 12-lead ECG by sporadic monitoring) to be entered into those studies. Accurate quantitative assessment of PAF burden, including brief and asymptomatic episodes, can only be achieved using continuous cardiac rhythm monitoring given the limitations inherent with intermittent monitoring.<sup>15</sup> In the TRENDS study, we took advantage of the long-term monitoring capability of modern implanted cardiac rhythm devices to provide an accurate continuous assessment of AT/AF burden over months to years of follow-up.

There are 2 major findings of the TRENDS study. First, there was a remarkably low TE rate in this large group of patients with moderately high mean CHADS<sub>2</sub> scores (2.2±1.2) and implanted pacemakers, ICDs, and CRT devices. Although the majority of participants (53%) and 30-day windows (76%) did not have any episodes of AT/AF, the rates of TE were low even among those with episodes of AT/AF and particularly low if TIAs were excluded. The second finding is that TE risk appears to be quantitatively linked to AT/AF burden. Low AT/AF burden (defined in our study as <5.5 hours on each of 30 preceding days) confers a TE risk similar to having no AT/AF, whereas an AT/AF burden of  $\geq$ 5.5 hours on any given day during the antecedent 30 days appears to confer a doubling of TE risk.

Other studies have also attempted to examine the relationship between AT/AF burden and outcome in device patients. Israel et al<sup>16</sup> showed that implanted devices provide a more sensitive and accurate measure of AT/AF burden than symptoms. A substudy of the MOde Selection Trial (MOST) reported that atrial high rate episodes lasting at least 5 minutes predicted a higher incidence of the composite outcome of death and nonfatal stroke.<sup>8</sup> Because of its small size (312 patients) and limitations in device memory in that era, the MOST investigators could not further quantify a burden value that raised the risk of the composite outcome of stroke and death. Furthermore, the majority of end points observed in the study were due to death, not stroke.

Capucci et al<sup>17</sup> analyzed 725 antitachycardia pacemakers with AT/AF burden recording capacity and found that AT/AF lasting  $\geq$ 24 hours conferred a 3-fold increase in TE risk compared with those with no AT/AF or episodes lasting <24 hours. The main limitation of this study is that patients with episodes <24 hours were combined with patients who had zero burden, making it difficult to specify a daily burden of brief AT/AF that raises the risk of TE.

The TRENDS study differs from these other studies in that it was a larger multicenter, prospective study, enrolling patients with devices capable of comprehensively recording AT/AF, including brief episodes. In TRENDS, the follow-up period was longer than previous studies and the primary end point was adjudicated TEs, which directly addresses the core issue of TE risk with brief episodes of PAF.

# Low Rate of TE in TRENDS

The rate of TE observed in TRENDS was far below the 4% annual rate anticipated on the basis of reports in AF patients

with average CHADS<sub>2</sub> scores  $\geq 2$  when the study was designed in 2003. Indeed, the low TE rate reported here prevented our planned primary analysis. Multiple recent studies have also reported lower than expected stroke rates even among patients with persistent AF.<sup>18,19</sup> Such low rates limit the potential benefit of anticoagulation and highlight the need to better predict the TE risk when considering long-term warfarin therapy. The results presented here are independent of warfarin use, suggesting that perhaps a finding of high AT/AF burden on device diagnostics is an additional piece of information to be used in conjunction with CHADS<sub>2</sub> score to determine need for anticoagulation.

# **AT/AF Burden**

The TRENDS data do not allow us to define a "safe" AT/AF burden threshold that confers a risk no greater than that of zero AT/AF burden. Although 30-day windows with maximal daily AT/AF burdens of <5.5 hours on each day in the window or <10.8 total hours in the prior 30 days yielded hazard ratios of 0.98 and 0.97, respectively, compared with zero AT/AF burden, the CIs were wide. Given the observed low TE rate, a much larger sample size would be needed to narrow the CI and to subdivide AT/AF burden into more groupings beyond the two created by the median. TRENDS results suggest that  $\geq$ 5.5 hours of AT/AF on a given day or total time of AT/AF  $\geq$ 10.8 hours in a 30-day window noted on routine interrogation of an implantable device, confers increased risk for TE.

# **Study Limitations**

The main limitation of our study is the unexpectedly low event rates. Low rates prevent precise definition of stroke risks associated with quantitatively defined AT/AF burden without a much larger sample size. The observed hazard ratio of 2.2 for high burden versus no AT/AF has a CI that includes 1.0. Therefore it remains possible, though unlikely, that our findings are due to random events.

Another limitation is the absence of electrograms to verify AF. In the TRENDS study, a pragmatic approach replicating clinical care used the nominal device settings (atrial rate >175 bpm lasting ≥20 seconds) to define an AT/AF episode. Previously published data suggest that excluding episodes <5 minutes eliminates most oversensing.<sup>20</sup> This limitation was addressed by completing an alternate analysis using a 5-minute threshold for AT/AF. With a 5-minute threshold, although the median values changed, the hazard ratios for low and high AT/AF burden compared with zero burden were nearly identical to those reported here (data not shown).

A final limitation is that although we accounted for use of anticoagulants in our regression models, we did not collect INR levels on patients treated with warfarin.

# Conclusions

TE risk is low in this group of patients despite a moderately high CHADS<sub>2</sub> risk score of 2.2. The TRENDS data suggest that AT/AF burden  $\geq$ 5.5 hours on any day in the most recent 30 days is associated with an approximate doubling of the risk of TE compared with zero AT/AF burden, after controlling for clinical stroke risk factors and antithrombotic use. Quantitative AT/AF burden detected by implanted devices may be a TE risk factor that is independent of standard clinical stroke risk factors. Further research is necessary to precisely identify the amount of AT/AF burden, in conjunction with other stroke risk factors that might merit medical intervention with antithrombotic therapy.

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#### References

- Bajai J, Avitall B. Atrial fibrillation. Curr Treat Options Cardiovasc Med. 2001;3:261–276.
- Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125.
- Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. JAMA. 1994;271:840–844.
- Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689–2696.
- Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy: Stroke Prevention in Atrial Fibrillation Investigators. J Am Coll Cardiol. 2000;35:183–187.
- ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical data standards. *Circulation*. 2004;109:3223–3243.
- Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, Connolly SJ. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. J Am Coll Cardiol. 2007;50: 2156–2161.

- Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, Cook J, Paraschos A, Love J, Radoslovich G, Lee KL, Lamas GA. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the atrial diagnostics ancillary study of the MOde Selection Trial (MOST). *Circulation*. 2003;107:1614–1619.
- Glotzer TV, Daoud EG, Wyse DG, Singer DE, Holbrook R, Pruett K, Smith K, Hilker CE. Rationale and design of a prospective study of the clinical significance of atrial arrhythmias detected by implanted device diagnostics: the TRENDS study. *J Interv Card Electrophysiol.* 2006; 15:9–14.
- Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001; 285:2864–2870.
- Fuster V, Ryden LE, Asinger AW, Cannom DS, Crijns HJ, Frye RL, Halperin JL, Kay GN, Klein WW, Levy S, McNamara RL, Prystowsky EN, Wann LS, and Wyse DG. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. *Circulation*. 2001;104: 2118–2150.
- Purerfellner H, Gillis AM, Holbrook R, Hettrick DA. Accuracy of atrial tachyarrhythmia detection in implantable devices with arrhythmia therapies. *Pacing Clin Electrophysiol*. 2004;27:983–992.
- Brunelli SM, Joffe MM, Israni RK, Yang W, Fishbane S, Berns JS, Feldman HI. History-Adjusted marginal structural analysis of the association between hemoglobin variability and mortality among chronic hemodialysis patients. *Clin J Am Soc Nephrol.* 2008;3:777–782.
- 14. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* 1994;154:1449–1457.
- Ziegler PD, Koehler JL, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. *Heart Rhythm.* 2006;3: 1445–1452.
- Israel CW, Grönefeld G, Ehrlich JR, Li YG, Hohnloser SH. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. J Am Coll Cardiol. 2004;43:47–52.
- Capucci A, Santini M, Padeletti L, Gulizia M, Botto G, Boriani G, Ricci R, Favale S, Zolezzi F, Di Belardino N, Molon G, Drago F, Villani GQ, Mazzini E, Vimercati M, Grammatico A. Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. J Am Coll Cardiol. 2005;46:1913–1920.
- Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Halperin JL, Horrow J, Olsson SB, Petersen P, Vahanian A. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA*. 2005;293:690–698.
- Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. 2003;290:2685–2692.
- Pollack WM, Simmons JD, Interian A, Atapattu SA, Castellanos A, Myerburg RJ, Mitrani RD. Clinical utility of intraatrial pacemaker stored electrograms to diagnose atrial fibrillation and flutter. *Pacing Clin Electrophysiol*. 2001;24:424–429.

# **CLINICAL PERSPECTIVE**

The clinical importance of atrial tachyarrhythmia (AT) episodes or atrial fibrillation (AF) detected by pacemakers and implantable cardioverter-defibrillators is currently unknown. In the practice of cardiology today, arrhythmia management devices are being implanted in increasing numbers of patients. With the increasing prevalence of these sophisticated devices, clinicians are confronted with accurate, quantitative and comprehensive memory for AT/AF events. Current evidence-based cardiology practice defines management strategies for AT/AF that is detected by conventional monitoring techniques, but these techniques are sensitive only for episodes that are frequent, prolonged, and/or symptomatic. It remains unknown if the same management strategies apply to brief and often asymptomatic episodes of AT/AF. In the research presented here, we made the first attempt to answer a question encountered frequently in pacemaker/implantable cardioverter-defibrillator clinics: Is there a critical level of AT/AF burden that increases the risk of thromboembolic events that is independent of other known risk factors? The data, although not definitive, suggest that there is such a quantitative relationship between AT/AF burden and thromboembolic events. Further research will improve the precision of the current estimate and define the impact of intervention with antithrombotic therapy.





**The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk: The TRENDS Study** Taya V. Glotzer, Emile G. Daoud, D. George Wyse, Daniel E. Singer, Michael D. Ezekowitz, Christopher Hilker, Clayton Miller, Dongfeng Qi and Paul D. Ziegler

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