Incidence of Newly Detected Atrial Arrhythmias via Implantable Devices in Patients With a History of Thromboembolic Events

Paul D. Ziegler, MS; Taya V. Glotzer, MD; Emile G. Daoud, MD; D. George Wyse, MD, PhD; Daniel E. Singer, MD; Michael D. Ezekowitz, MD, PhD; Jodi L. Koehler, MS; Christopher E. Hilker, MS

**Background and Purpose**—Evidence of atrial tachycardia/atrial fibrillation (AT/AF) is often sought in patients with ischemic stroke or transient ischemic attack. We studied patients with previous thromboembolic events (TE) who were implanted with devices capable of continuous arrhythmia monitoring to comprehensively quantify the incidence and duration of newly detected AT/AF.

**Methods**—This study represents a subgroup analysis of the TRENDS trial, which included patients with clinical indications for pacemakers or defibrillators and ≥1 stroke risk factors (heart failure, hypertension, age 65 or older, diabetes, or previous TE). A history of AF was not required. All implanted devices were capable of continuously monitoring the cumulative time spent in AT/AF each day. This analysis focuses primarily on the incidence and duration of newly detected AT/AF (defined as ≥5 minutes of AT/AF on any day) in patients with previous TE, no documented history of AF, and no warfarin or antiarrhythmic drug use.

**Results**—A total of 319 patients had a history of TE and ≥1 day of device data. Patients with a documented history of AF (n=80), warfarin use (n=56), or antiarrhythmic drug use (n=20) were excluded from analysis. Of the remaining 163 patients, newly detected AT/AF was identified via the device in 45 patients (28%) over a mean follow-up of 1.1±0.7 years. AT/AF recurred infrequently, with only 12 patients experiencing AT/AF on >10% of follow-up days.

**Conclusion**—Newly detected episodes of AT/AF were found via continuous monitoring in 28% of patients with previous TE. Most episodes would not have been detected by standard intermittent monitoring techniques. (Stroke. 2010;41:00-00.)

**Key Words:** ambulatory electrocardiography ■ atrial fibrillation ■ diagnostic methods ■ stroke

Evidence of atrial fibrillation (AF) is often sought in patients who survive an ischemic stroke or TIA because the presence of AF has important etiologic and therapeutic implications. However, patient symptoms are insensitive and nonspecific for identifying paroxysmal atrial tachycardia/atrial fibrillation (AT/AF),1,2 whereas rhythm monitoring with external systems is hindered by intermittent sampling3 and patient compliance issues.4 In contrast, continuous monitoring has been shown to be significantly more effective for identifying patients with asymptomatic or intermittent AT/AF recurrences,5,5 and the daily amount of AT/AF has been related to the risk of thromboembolic events (TE) in patients receiving cardiac rhythm devices.6

Previous studies7–10 have investigated the role of short-term (up to 30 days) external monitoring for the identification of undiagnosed AF in patients with previous stroke. Because these previous studies essentially show that the likelihood of finding AT/AF increases with longer durations of monitoring, we hypothesized that continuous monitoring would find even more AT/AF. Therefore, we studied a cohort of patients who required implantation of a cardiac rhythm device with a history of TE to quantify the incidence and duration of newly detected AT/AF (NDAF). We also examined NDAF in patients without a previous TE but with other risk factors for stroke.

**Subjects and Methods**

The study population represents a group of patients that was enrolled in a larger study (TRENDS). The design11 and the main results6 of the TRENDS study have been previously reported. In brief, TRENDS was a prospective, observational study that enrolled patients with a clinical indication for a pacemaker or implantable cardioverter defibrillator and at least 1 of the following stroke risk factors: congestive heart failure, hypertension, age 65 or older, diabetes, or previous stroke/TIA. Physicians were not required to have a history of AF, and warfarin use was prescribed by the patient’s managing physician. Physicians were encouraged to follow published guidelines for the use of antithrombotic therapy.12 The TRENDS study reported that TE risk is a quantitative function of arrhythmia burden among the overall population of patients indicated for a cardiac rhythm device. The study protocol was approved.

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by the Institutional Review Board of each participating center and all patients provided informed consent.

The purpose of the current retrospective subanalysis was to quantify the incidence and duration of NDAF through the use of continuous monitoring by implanted cardiac devices. This substudy focuses primarily on those patients enrolled in TRENDS who had a history of stroke or TIA; however, data are also presented on patients without previous TE (but with other stroke risk factors, including congestive heart failure, hypertension, age 75 or older, and diabetes) for comparison. Patients with a documented history of AF were excluded. Similarly, patients using warfarin or antiarrhythmic drugs were also excluded because this may indicate the existence of undocumented but diagnosed AF. Patients were also required to have at least 1 day of device-stored data available for analysis.

Definitions and Device Capabilities
AT/AF burden was defined as the total cumulative duration of AT/AF detected by the device in a given day. AT/AF burden may consist of multiple episodes on a single day or a portion of a single episode that spans multiple days. The implanted devices were capable of continuously monitoring AT/AF burden for up to 14 months. Data were extracted from the devices via telemetry at office visits. Follow-up visits were scheduled with sufficient frequency to ensure data continuity. Previous studies utilizing devices with similar detection algorithms have shown >95% sensitivity and specificity for detection of atrial arrhythmia episodes and measurement of atrial arrhythmia burden.

NDAF was defined as at least 5 minutes of atrial arrhythmia recorded by the device on any day during the study. In this analysis, only days with at least 5 minutes of AT/AF were considered, because this duration excludes most episodes of atrial oversensing leading to false-positive recordings of AF. Because our goal was to study the readily available diagnostic data within the device memory, we did not attempt to distinguish between episodes of atrial tachycardias, atrial flutter, and atrial fibrillation. Furthermore, intracardiac electrograms were not available for each episode because of device memory constraints.

Statistical Methods
We quantified the percentage of patients with previous TE, no documented history of AF, and no warfarin or antiarrhythmic drug use who experienced NDAF. The percentage of patients having ≥5 minutes, ≥6 hours, or ≥24 hours of AT/AF burden on a single day or 2 and 7 consecutive days of AT/AF were tabulated. Time to identification of NDAF was computed using Kaplan-Meier survival estimates and compared with the log-rank test. We also tabulated the number of patients with recurrences and the timing of recurrences among those with at least 1 episode of AT/AF to illustrate the difficulties with intermittent monitoring, which is defined as the use of an externally worn continuous cardiac rhythm monitor for up to 30 days. Demographics were compared among patients with previous TE who were found to have NDAF vs those with no AT/AF. The incidence of NDAF was also computed among patients without a previous TE (but with other stroke risk factors) and compared to patients with a previous TE.

Continuous variables are presented as means±SD or medians and interquartile range, as appropriate, and categorical variables are presented as percentages. Categorical variables were compared using the χ² test and continuous variables were compared using a Wilcoxon rank-sum test. A significance level of 0.05 was used.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
Patient Cohort
A total of 3045 patients were enrolled in the TRENDS study from 116 centers. From this population, 319 patients had a history of previous TE and device data available for analysis. Patients with a documented history of AF (n=80), warfarin use (n=56), or antiarrhythmic drug use (n=20) were excluded from the analysis. Among the remaining 163 patients (followed-up a mean of 1.1±0.7 years), the average CHADS₂ score was 4.1±0.8, reflecting their high risk for stroke recurrence. The median time from the previous TE to enrollment in the study was 39 (12–73) months. Additional characteristics for the 163 patients included in this subgroup analysis are presented in the Table. Patients with a previous TE who were found to have NDAF were more likely to have heart failure vs those with no detection of AT/AF.

Incidence of NDAF
NDAF was identified by the implantable device in 45 of 163 patients (28%) over the course of follow-up. Detection of NDAF occurred in pacemaker (n=20) and defibrillator (n=25) patients in a similar proportion to their prevalence in the study.

There were 1428 patients in the overall TRENDS study population without a history of previous TE, documented AF, warfarin, or antiarrhythmic drug use and who had device data available (Table). Over a mean follow-up of 1.1±0.7 years, NDAF was found in 432 patients (30%), which was essentially the same incidence rate as for those with a history of previous TE (P=0.49).

AT/AF Burden in NDAF Patients
NDAF patients often experienced individual or consecutive days with considerably greater amounts of AT/AF than the minimum threshold of 5 minutes (Figure 1). For example, 25 patients (56% of NDAF patients with previous TE) had at least 6 hours of AT/AF on a single day. Over the entire study period, the average daily AT/AF burden in NDAF patients with previous TE was 1.8±4.0 hours, whereas the median daily AT/AF burden was 0.08 (interquartile range [IQR], 0.01–1.23) hours. The day with maximal AT/AF duration was greater among NDAF patients with previous TE (median, 10.8; IQR, 2.4–23.9 hours) compared to NDAF patients without previous TE (median, 5.9; IQR, 1.2–20.4 hours), but the difference did not reach statistical significance (P=0.29). Figure 2 shows the distribution of the percentage of follow-up days in which at least 5 minutes of AT/AF was detected by the device among NDAF patients. For example, 73% of NDAF patients with previous TE experienced episodes of AT/AF on <10% of follow-up days. Only 11% of NDAF patients with previous TE experienced AT/AF on a majority of follow-up days, a frequency needed to be reliably detected by random intermittent monitoring.

Time to Detection of NDAF
The time from implantation of the continuous monitoring device until first detection of NDAF is presented in the survival curve in Figure 3. The median time from enrollment in the study to identification of NDAF was 1.7 (IQR, 0.4–6.7) months among previous TE patients with NDAF and 2.0 (IQR, 0.3 to 5.4) months among nonprevious TE patients with NDAF (log-rank, P=0.56). The continuous arrhythmia data from the device allowed us to simulate the percentage of patients who would have been identified as having NDAF if this rhythm information had only been available on the subset of days monitored by traditional methods. Only 3% of patients would have been identified via a single 24-hour Holter monitor if performed immediately at
the time of enrollment, whereas only 4% would have been identified via 48-hour Holter monitoring performed at the time of enrollment in the study. Increasing the initial monitoring duration to 7, 21, or 30 consecutive days would have identified 6%, 9%, or 11% of previous TE patients, respectively. In contrast, continuous arrhythmia monitoring over the follow-up period resulted in significantly greater identification of NDAF (28% of patients) compared to these common intermittent monitoring regimens ($P<0.001$).

### Table. Baseline Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Previous TE Patients</th>
<th>Other Risk Factor Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients With NDAF</td>
<td>Patients Without NDAF</td>
</tr>
<tr>
<td>Age, yr</td>
<td>74.0±9.1</td>
<td>72.8±9.9</td>
</tr>
<tr>
<td>Gender, male</td>
<td>32 (71.1%)</td>
<td>74 (62.7%)</td>
</tr>
<tr>
<td>CHADS$_2$ score</td>
<td>4.2±0.8</td>
<td>4.1±0.8</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>26 (57.8%)*</td>
<td>47 (39.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (84.4%)</td>
<td>100 (84.7%)</td>
</tr>
<tr>
<td>Age &gt;75 yr</td>
<td>20 (44.4%)</td>
<td>52 (44.1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (35.6%)</td>
<td>48 (40.7%)</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>45 (100%)</td>
<td>118 (100%)</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>20 (44.4%)</td>
<td>71 (60.2%)</td>
</tr>
<tr>
<td>SA node conduction problems</td>
<td>13 (28.9%)</td>
<td>47 (39.8%)</td>
</tr>
<tr>
<td>AV conduction problems</td>
<td>7 (15.6%)</td>
<td>20 (16.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0%)</td>
<td>4 (3.4%)</td>
</tr>
<tr>
<td>Implantable cardioverter defibrillator</td>
<td>25 (55.6%)</td>
<td>47 (39.8%)</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>19 (42.2%)</td>
<td>34 (28.8%)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>6 (13.3%)</td>
<td>13 (11.0%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>136.3±22.3</td>
<td>136.8±22.3</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>34 (75.6%)</td>
<td>81 (68.6%)</td>
</tr>
<tr>
<td>Class I/III antiarrhythmics</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>28 (62.2%)</td>
<td>78 (66.1%)</td>
</tr>
<tr>
<td>Antipllatelets</td>
<td>21 (46.7%)</td>
<td>58 (49.2%)</td>
</tr>
<tr>
<td>Statins</td>
<td>28 (62.2%)</td>
<td>78 (66.1%)</td>
</tr>
</tbody>
</table>

* $P<0.05$, NDAF vs no NDAF in patients with previous TE.
† $P<0.05$, NDAF vs no NDAF in patients with other risk factors.
AV indicates atrioventricular; SA, sino-atrial.

### Discussion

Detection of AF in patients at high risk for stroke will strongly influence anticoagulation decisions. The present prospective study, using continuous arrhythmia monitoring, detected NDAF in 28% of patients with previous TE over a mean follow-up of 1.1 years. The majority of NDAF was identified by monitoring for up to 7 days, but increasing the monitoring duration to 7, 21, or 30 days would have identified an additional 6%, 9%, or 11% of patients, respectively. Continuous monitoring over the follow-up period resulted in significantly greater identification of NDAF (28% of patients) compared to intermittent monitoring regimens ($P<0.001$).
identified >30 days after study entry. In a small percentage of patients, NDAF was present during most of the follow-up period but the majority had infrequent episodes. The latter episodes of NDAF would have been missed entirely, even with prolonged durations of traditional ECG monitoring.

### Incidence of NDAF

Whereas we found a substantially higher percentage of previous stroke patients having NDAF overall compared to other studies, our rates of detection were similar when comparing equivalent monitoring periods. Jabaudon et al identified NDAF in 5.0% of patients via 24-hour Holter monitoring, whereas we identified NDAF in 3.1% of patients within the same 24-hour period. Bansil et al found NDAF via 48-hour Holter in 4.0% of patients compared to 4.3% in our study over the same period. Jabaudon et al also found NDAF in 8.1% of patients via Holter recordings within the first 7 days compared to 6.1% in the present study.

Two previous studies evaluated the incidence of occult AF in patients with cryptogenic stroke. Using 21-day and 30-day external event monitors, NDAF was detected in >20% of patients when inpatient telemetry and electrocardiography did not detect AF. However, the majority of AF episodes detected in these studies were <30 seconds in duration, thereby failing to satisfy the definition of an AF “episode” in recently published AF consensus statements. In the present study, 60% of NDAF patients were identified beyond the initial 30 days of the study, potentially adding to the value of long-term arrhythmia monitoring.

In this analysis, we found a similar rate of NDAF in patients with stroke risk factors regardless of the presence of previous TE. This may indicate that the presence of any stroke risk factors is associated with a high likelihood of finding previously unknown AT/AF, particularly in a population with cardiac conditions necessitating device implantation. However, there was a tendency (not significant) for the duration of maximal daily AT/AF burden to be longer among those with a previous TE.

### AT/AF Burden

Several previous studies have examined the relationship between AT/AF burden and outcome in cardiac rhythm device patients. A substudy of the MOde Selection Trial (MOST) reported that the composite end point of nonfatal stroke and death was significantly higher in patients having at least 5 minute episodes of high rate atrial arrhythmias. This finding, in part, contributed to our selection of the 5-minute threshold for the definition of NDAF.

The TRENDS study recently reported that an arrhythmia burden >5.5 hours on any of 30 previous days appeared to double the risk of TE compared to no burden, based on a 20-second definition for AT/AF. In a subanalysis of the present patients with previous TE, we found that 58% of NDAF patients met the >5.5-hour criterion for elevated TE risk. Taken together, these findings indicate that clinically important amounts of AT/AF occur in a substantial proportion of patients with previous TE but no previous diagnosis of AF.

By defining NDAF as a minimum of 5 minutes of device-detected AT/AF on a given day, it is possible that we may have underreported the true incidence of NDAF. Implantable devices typically require atrial arrhythmias to persist for >30 seconds for detection to occur. Relying solely on device detection of any AT/AF as the threshold for diagnosing NDAF would have increased the incidence of NDAF among those with previous TE to 36% in the present analysis. However, such short durations of AT/AF are more likely to include false-positive detections.

Previous studies have shown that the probability of detecting AT/AF via intermittent monitoring decreases as the amount of AT/AF present decreases. Without continuous arrhythmia monitoring, identification of patients with low AT/AF burden may be delayed. In the present study, we found that the majority of NDAF patients (73%) had AT/AF on <10% of follow-up days, making it highly unlikely to be detected by standard monitoring techniques. Whereas we obtained continuous heart rhythm monitoring using im-
planted cardiac devices, small subcutaneous devices are now available to provide similar heart rhythm surveillance. These may facilitate the detection of AT/AF in high-risk patients, such as those with cryptogenic stroke, potentially leading to improved prevention of recurrent stroke.

Limitations
This study was conducted primarily in patients with a remote previous TE who had a clinical indication for an implantable pacemaker or defibrillator; therefore, these results may not be representative of all patients with previous TE and, in particular, may not apply to patients with cryptogenic stroke in whom monitoring is typically performed in close proximity to the TE. However, the rates of NDAF detected over the initial few days or weeks in this study were similar to previous studies in nondevice patients. Another limitation is that some patients included in our analysis may have had AF that was known but not documented prior to study enrollment. However, our exclusion of patients who were already using warfarin or antiarrhythmic drugs likely excluded the majority of patients with known previous AF. It is also possible that AF may have been detected clinically during follow-up, thereby reducing the incremental diagnostic value of continuous monitoring. However, because only 11% of patients had AT/AF on the majority of follow-up days, this is unlikely except for those with the greatest AT/AF burden. A final limitation is that the absence of electrograms for all episodes precluded us from verifying the precise diagnosis of the atrial arrhythmias. Previous reports, though, suggest that most arrhythmia oversensing that can result in false-positive detection of AT/AF is eliminated by excluding episodes <5 minutes,14 which was the duration criteria for the current study.

Summary
In a cohort of patients with previous TE, no known AF, and requiring a cardiac rhythm device, 28% of patients were identified as having NDAF via a device with continuous monitoring capabilities. Whereas AT/AF occurred on <10% of follow-up days in 73% of NDAF patients, it also persisted for at least 6 hours on at least 1 day in the majority of NDAF patients. These finding highlight not only the difficulty of detecting AT/AF with traditional methods but also the importance of identifying AT/AF in this population.

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Disclosures
P.D.Z., J.L.K., and C.E.H. are employees and stockholders of Medtronic. T.V.G. is a consultant for Medtronic and a speaker for Medtronic, St. Jude Medical, and Boston Scientific. D.G.W. is a consultant for Medtronic and a speaker for Medtronic, St. Jude Medical, and Boston Scientific. C.E.H. is a consultant for Medtronic. M.E.D. is a consultant for Medtronic.

References
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通过植入装置测定血栓栓塞病史患者的新发房性心律失常发生率

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背景和目的: 我们常在缺血性卒中或短暂性脑缺血发作的患者中找到房性心动过速/心房颤动（AT/AF）的证据。我们对既往有血栓栓塞（TE）事件的患者，通过植入持续监测心律失常的装置来全面地量化新发现的AT/AF的发生率和持续时间。

方法: 本研究是TRENDS研究的亚组分析，TRENDS研究对象为有起搏器或除颤器使用临床指征并有至少一项卒中危险因素（心力衰竭、高血压、年龄≥65岁、糖尿病、有TE事件）的患者。并不要求有心房颤动病史。植入装置可以每天不间断地监测心动过速或心房颤动的累积时间。研究着重于分析既往有血栓栓塞事件，但无心房颤动史、未使用华法令或抗心律失常药物的患者中，新确诊为AT/AF（定义为一天AT/AF的持续时间≥5分钟）的发生率和持续时间。

结果: 共319名患者有TE病史和≥1天的植入装置记录数据，排除其中有明确AF病史（n=80）、应用华法令（n=56）或应用抗心律失常药物（n=20）者，余163名患者。其中，在平均1.1±0.7年的随访期内，通过装置发现了45名（28%）患者有AT/AF发作。AT/AF复发很少见，只有12名患者在>10%的随访时间里发生AT/AF。

结论: 通过连续监测发现28%的TE患者中有AT/AF发作。绝大多数AT/AF发作不能被普通的间断监测技术所发现。

关键词: 便携式心电监护仪, 心房颤动, 诊断方法, 卒中

(Stroke. 2010;41;256-260. 李兰玉 译 李焰生 校)

对于缺血性卒中或短暂性脑缺血发作（TIA）的存活患者，常需寻找心房颤动（AF）的证据，因为AF的出现有重要的病因学和治疗学意义。但是，通过患者的症状或体征来发现阵发性心动过速或心房颤动既不敏感也非特异[1,2]，通过外部设备进行心律监测存在间断取样[3]和患者依从性不佳[4]的问题。相反，持续地监测已被证明能显著地识别无症状患者或间歇性AT/AF复发[5,6]，且在接受心脏节律装置的患者中，AT/AF每天发作的总量与TE发生的风
险存在相关性[6]。

以往的研究[7,10]观察了短期外部监测（30天内）对在有卒中史的患者中发现未诊断AF的作用。这些既往研究的基本发现是持续监测的时间越长，发现AT/AF的可能性越大。我们推测持续监测可以发现更多的AT/AF，因而选择一组有TE病史并需植入心脏节律装置的患者，以量化地识别新发现AT/AF（Newly Detected AT/AF, NDAF）的发生率和持续时间。同时，检测之前没有TE史但有其他卒中危险因素的患者的NDAF。

研究对象和方法

性心力衰竭、高血压、年龄≥65岁、糖尿病或既往卒中/TIA病史。患者不一定有AF病史，由其经治医生负责华法令治疗。鼓励医生遵循指南[12]给予患者抗栓治疗。TRENDS研究表明，在所有需要安装心脏节律装置的患者人群中，TE风险可定量心律失常的负担。该研究得到所有参与中心的审查委员会的许可，所有入选患者知情同意。

本次回顾性亚组分析的目的是通过植入性心脏装置进行持续监测来量化NDAF的发生率和持续时间。亚组分析主要关注那些有卒中/TIA病史的患者，但也提供了没有TE病史（但有其他卒中危险因素，如充血性心衰、高血压、大于75岁、糖尿病）患者的证据，以作为对照。有确定AF病史者排除，正在服用华法令和抗心律失常药物的患者也被排除，因为这些患者可能没有被仪器发现但却被诊断为AF。入选患者应有至少1天的装置记录数据以便进行分析。

定义和装置功能

AT/AF负荷定义为1天中被装置监测的AT/AF的总时间。AT/AF负荷可由1天中的多次发作组成，也可以是持续多日的1次发作。植入的装置可以持续监测AT/AF负荷将近14个月。在办公室里通过遥测技术可将数据资料从装置里提取出来。安排足够次数的随访，以保证数据资料的连续性。以往的研究已证明使用相似的监测方法，发现房性心律失常发作负荷的敏感性和特异性均>95%[13]。

NDAF定义为在研究的任意1天内通过设备发现的持续至少5分钟的房性心律失常。本次分析中，只有持续至少5分钟的AF或AT被承认，这样可以很大程度地避免将房性过度感知误认为AF发作[14]。本研究的目标是研究仪器所记录数据中容易获得的诊断性数据，因此并不试图去鉴别房性心动过速、心房扑动和心房颤动的发作。此外，由于仪器记录数据的局限，使我们不能记录每次发作时的心电图。

统计方法

我们量化有TE病史、无明确AF病史、不使用华法令或抗心律失常药物的患者中，出现NDAF的百分比。AT/AF在1天，2天及7天内持续≥5分钟、≥6小时、≥24小时的百分比用图表分析。通过Kaplan-Meier生存曲线分析发生NDAF的时间，并用对数秩检验比较。我们也列表显示在有过至少1次AT/AF发作的患者中，AT/AF复发的患者数和复发的时间间隔，以说明间断性监测的难度。间断性监测是指通过体表配带心律检测器持续监测最多30天。对之前有或无NDAF的TE患者进行人口统计学比较，同时比较没有TE病史（但有其他卒中危险因素）的患者与有TE病史者的NDAF发生率。

连续变量用均值±标准差或中位数和四分位间距表示，分类变量用χ2检验进行比较，连续变量使用Wilcoxon秩和检验进行比较。使用α=0.05的显著性水平。

作者获得了全部的数据资料，并对数据资料完整性负责。所有作者都阅读并同意文稿。

结果

患者资料

来自116个中心共有3045名患者入选TRENDS研究。在这些人群中，有319名患者有TE病史和装置记录数据资料可用于分析。排除了有明确AF病史（n=80）、应用华法令（n=56）或应用抗心律失常药物（n=20）的患者后，余163名患者中（平均随访时间是1.1±0.7年），平均CHADS2分数为4.1±0.8，反映了卒中再发风险较高。发生TE事件至登记入研究的时间中位数为39(12-73)个月。163名患者的其它资料见表。有TE病史的患者中，有NDAF的患者比无AT/AF的患者更易发生心力衰竭。

NDAF的发生率

在随访期间，163名患者中有45名（28%）通过植入性装置诊断为NDAF。起搏器植入（n=20）患者和除颤器植入（n=25）患者在本次研究中有相似的NDAF患病率。

全部TRENDS研究人群中，有1428名患者有TE病史、无明确诊断的AF、未应用华法令或抗心律失常药物，且有装置记录数据资料。在平均1.1±0.7年的随访期间，432名患者（30%）发现了NDAF，与有TE病史患者的发病率相同，两者间无统计学差异（P=0.49）。

NDAF患者的AT/AF负荷

研究发现NDAF患者在个别或连续测量日内有大量超过最小临界值5分钟的AT/AF（图1）。例如，25名患者（占有TE病史的NDAF患者的56%），在1天中至少有6小时的AT/AF时间。在整个研究期间，有TE病史的NDAF患者的每日AT/AF负荷平均数是1.8±4.0小时，而每日AT/AF负荷的中位数是0.08小时（四分位数间距[IQR]是0.01-1.23）。有TE
表 基线人口学资料

<table>
<thead>
<tr>
<th>参数</th>
<th>有 NDAF (n=45)</th>
<th>无 NDAF (n=118)</th>
<th>有 NDAF (n=432)</th>
<th>无 NDAF (n=996)</th>
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<tr>
<td>年龄 (岁)</td>
<td>74.0±9.1</td>
<td>72.8±9.9</td>
<td>70.8±12.1†</td>
<td>69.7±11.5</td>
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<td>性别 (男性)</td>
<td>32 (71.1%)</td>
<td>74 (62.7%)</td>
<td>299 (69.2%)</td>
<td>647 (65.0%)</td>
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<td>CHADS2 评分</td>
<td>4.2±0.8</td>
<td>4.1±0.8</td>
<td>2.0±0.9</td>
<td>1.9±0.9</td>
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<td>充血性心力衰竭</td>
<td>26 (57.8%)*</td>
<td>47 (39.8%)</td>
<td>226 (52.3%)</td>
<td>482 (48.4%)</td>
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<td>高血压</td>
<td>38 (84.4%)</td>
<td>100 (84.7%)</td>
<td>325 (75.2%)</td>
<td>733 (73.6%)</td>
</tr>
<tr>
<td>年龄 &gt;70 岁</td>
<td>20 (44.4%)</td>
<td>52 (44.1%)</td>
<td>187 (43.3%)†</td>
<td>374 (37.6%)</td>
</tr>
<tr>
<td>糖尿病</td>
<td>16 (35.6%)</td>
<td>48 (40.7%)</td>
<td>120 (27.8%)†</td>
<td>341 (34.2%)</td>
</tr>
<tr>
<td>起搏器</td>
<td>45 (100%)</td>
<td>118 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>房室结传导阻滞</td>
<td>13 (28.9%)</td>
<td>47 (39.8%)</td>
<td>111 (25.7%)</td>
<td>263 (26.4%)</td>
</tr>
<tr>
<td>房室结传导阻滞</td>
<td>7 (15.6%)</td>
<td>20 (16.9%)</td>
<td>67 (15.5%)</td>
<td>158 (15.9%)</td>
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<td>其他</td>
<td>0 (0.0%)</td>
<td>4 (3.4%)</td>
<td>13 (3.0%)</td>
<td>3 (2.3%)</td>
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<td>植入式心律除颤器</td>
<td>26 (55.6%)</td>
<td>47 (39.8%)</td>
<td>241 (55.8%)</td>
<td>552 (55.4%)</td>
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<td>一级预防</td>
<td>19 (42.2%)</td>
<td>34 (28.8%)</td>
<td>191 (44.2%)</td>
<td>449 (45.1%)</td>
</tr>
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<td>二级预防</td>
<td>6 (13.3%)</td>
<td>13 (11.0%)</td>
<td>50 (11.6%)</td>
<td>103 (10.3%)</td>
</tr>
<tr>
<td>收缩压, mmHg</td>
<td>136.3±22.3</td>
<td>136.8±22.3</td>
<td>133.8±22.6</td>
<td>133.3±22.7</td>
</tr>
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<td>冠心病</td>
<td>34 (75.6%)</td>
<td>81 (68.6%)</td>
<td>267 (61.8%)</td>
<td>636 (63.9%)</td>
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<td>I/III 类抗心律失常药物的使用</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>华法令</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>阿司匹林</td>
<td>28 (62.2%)</td>
<td>78 (66.1%)</td>
<td>287 (66.4%)</td>
<td>691 (69.4%)</td>
</tr>
<tr>
<td>抗血小板药物</td>
<td>21 (46.7%)</td>
<td>58 (49.2%)</td>
<td>94 (21.8%)</td>
<td>241 (24.2%)</td>
</tr>
<tr>
<td>他汀类药物</td>
<td>28 (62.2%)</td>
<td>78 (66.1%)</td>
<td>233 (53.9%)</td>
<td>578 (58.0%)</td>
</tr>
</tbody>
</table>

*P<0.05，既往有血栓栓塞事件的患者中，有 NDAF vs 无 NDAF
†P<0.05，存在其他危险因素的患者中，有 NDAF vs 无 NDAF

病史的 NDAF 患者中 AT/AF 最长时间（中位数 10.8；IQR，2.4-23.9 小时）大于无 TE 病史的 NDAF 患者（中位数 5.9；IQR，1.2-20.4 小时），但两者的差异无统计学意义 (P=0.29)。图 2 显示了在随访期间 NDAF 患者通过装置发现至少有持续 5 分钟的 AT/AF 的天数的分布比例。例如，73% 的有 TE 病史的 NDAF 患者发生 AT/AF 发作的天数小于随访期天数的 10%。只有 11% 的有 TE 病史的 NDAF 患者在随访期的大部分时间里发生 AT/AF 发作，其频率需通过随机间隔监测仪进行可靠检测。

**发现 NDAF 的时间**

图 3 的存活曲线显示了从植入持续监测装置至

![图 1](超近 AT/AF 负荷阈值的 NDAF 患者百分比)

![图 2](NDAF 者 AT/AF 发作天数百分比的分布)
首次发现 NDAF 的时间。从登记研究至发现 NDAF 的时间的中位数，在有 TE 病史的 NDAF 患者中是 1.7(IQR, 0.4-6.7) 个月，而在无 TE 病史的 NDAF 患者中是 2.0(IQR, 0.3-5.4) 个月 (秩和检验，P=0.56)。由装置获得的持续心律失常的数据资料，使我们可模拟通过传统方法获得的部分心律失常信息而诊断为 NDAF 的患者的百分比。在试验当日，仅 3% 患者可以通过 24 小时 Holter 监测确诊，仅 4% 的患者可通过 48 小时的 Holter 监测确诊。增加监测时间为 7、21 或 30 个连续日，则可分别确诊 6%、9% 和 11% 的有 TE 病史的患者。相比而言，在随访期间持续心律失常监测与普通间断心律失常监测相比，前者可获得更高 (P<0.001) 的 NDAF 确诊率 (28% 的患者)。

讨论
卒中高危患者 AF 的诊断将大大影响抗凝治疗的决策。前前瞻性研究使用持续心律失常监测，在平均 1.1 年的随访期间，发现 28% 的有 TE 病史的患者有 NDAF。大部分 NDAF 是在患者入选试验 30 天后被诊断。除了小部分患者的 NDAF 在随访的大部分时间里存在，绝大多数则为偶尔发作。后一种 NDAF 发作常常会被完全错过，尽管延长了传统的 ECG 监测的时间。

NDAF 的发生率
与以往的研究相比，本研究发现卒中病人 AF 患者的 NDAF 的百分率高很多。如检查时间相

当，本研究发现的比率与其他研究相似。Jabaudon 等 [8] 通过 24 小时 Holter 监测诊断出 5% 的有 NDAF，而我们在相同的 24 小时时间里发现 3.1% 的有 NDAF。Bansil 等 [9] 通过 48 小时 Holter 监测发现 4.0% 的有 NDAF，而我们在相同的持续时间里发现 4.8% 的有 NDAF。Jabaudon 等 [8] 通过入选后第 1 个 7 天的 Holter 监测发现 8.1% 的有 NDAF, 而本研究发现 6.1% 的患者有 NDAF。

两项先前研究评估了病因不明的卒中患者的 AF 发生率。当住院患者监测技术和心电描记法不能诊断 AF 时，使用 21 天 [7] 和 30 天 [10] 的外部监测仪，约 20% 的患者被诊断出 NDAF。但是，这些研究发现的大部分 AF 发作的持续时间 <30 秒，因此根据最近公布的 AF 专家共识 [15]，它们不符合 AF “发作” 的定义。本研究里，60% 的 NDAF 是在研究开始 30 天后才被发现，提示了长期心律失常监测的意义较大。

在该项分析中，我们发现有卒中危险因素的患者，无论有无 TE 病史，其 NDAF 的发生率相似。这表明任何卒中危险因素的出现与先前未知的 AT/AF 的存在有很高的相关性，尤其是在需植入心脏装置的患者中。但是，有 TE 病史的患者有最大 AT/AF 日负荷的持续时间更长的趋势（不显著）。

AT/AF 负荷
先前的一些研究调查了使用心脏节律装置患者中 AT/AF 负荷与结局间的关系。模式选择试验 (Mode Selection Trial, MOST) 的一项亚组分析显示非致命性
卒中和死亡的复合终点在有至少5分钟的快速房性心律失常发作的患者中明显增高。这项发现是我们定义NDAF为5分钟临界值的原因。

TRENDS研究近来报道，在定义AT/AF时间为20秒的基础上，如果之前30天内有任一天出现心律失常负荷≥5.5小时，会使TE发生的风险加倍。对本研究中有过植入心脏装置进行持续心脏节律监测，目前也定义为诊断。综合考虑，这些发现表明，在相当部分有TE病史但先前未诊断为AF患者中，AT/AF发生的量有重要的临床意义。

由于定义NDAF为在给定的一天内，装置监测到的至少持续5分钟的AT/AF，我们可能会低估NDAF真正发生率。植入装置需要房性心律失常持续至少约30秒才能被发现。目前的分析表明，在有TE病史的患者中，单独依靠任一次AT/AF发作作为诊断NDAF的临界值，可能会增加NDAF的发生率至36%。但是，如此短暂的AT/AF的持续时间，可能会包含假阳性的发作。

先前研究表明，当AT/AF发作的次数减少时，间隔监测诊断AT/AF的可能性也减少。缺乏持续心律失常监测，AT/AF负荷低的患者，可能被延误诊断。在本研究中，我们发现大部分NDAF患者(73%)在<10%的随访期间内有AT/AF发作，这使得标准的监测技术很难发现。我们在此研究中使用了植入心脏装置进行持续心脏节律监测，目前也可用小型的皮下装置提供相似的心脏节律监测。这些为高危患者如原因不明的卒中患者提供便利，可能使得预期卒中再发得到改善。

局限性

本研究主要是在有远期TE病史，并有应用起搏器或除颤器的临床指征的患者中进行；因此，这些结果可能并不能反应有TE病史的所有患者的全貌，特别是，可能不适用于原因不明的卒中的患者，因这些患者的监测时间极为接近TE。但是，在本研究最初的几天或几周内，NDAF的诊断率与先前研究中未植入装置的患者的诊断率相似。另一项不足是我们分析的一些患者可能存在有AF，只是在入选试验之前没有被记录。但是，我们排除了应用过华法令或抗心律失常药物的患者，可以排除大部分有AF病史的患者。还有可能是在随访期间，根据临床特征诊断AF，因而减弱了持续监测的诊断价值。但是，由于只有11%的患者在随访的大部分时间里发生AT/AF，上述可能性不太大，除非患者的AT/AF负荷值大。最后一个局限是，由于缺少发作时心电图使得我们不能对房性心律失常做出准确判断。但是先前的报道显示通过排除<5分钟的发作(目前研究中使用的持续时间标准)，可排除大部分会导致AT/AF假阳性诊断的心律失常敏感性过高的情况。

总结

在有TE病史、无AF且需心脏节律装置的患者人群中，28%的患者通过持续监测装置被诊断为NDAF。然而，73%的NDAF患者在<10%的随访期间内发生AT/AF，大部分NDAF患者至少1天内有不小于6小时的AT/AF发作。这些发现不仅强调了通过传统方法诊断AF/AF的困难性，也强调了在这些人中确认AT/AF的重要性。

参考文献