Prolonged Rhythm Monitoring for the Detection of Occult Paroxysmal Atrial Fibrillation in Ischemic Stroke of Unknown Cause

Raymond C.S. Seet, MD; Paul A. Friedman, MD; Alejandro A. Rabinstein, MD

Atrial fibrillation (AF), commonly encountered in patients with ischemic stroke and transient ischemic attack (TIA), confers a 5-fold increased risk of ischemic stroke. AF-related strokes are associated with an ≈50% increased risk of disability and 60% increased risk of death at 3 months compared with strokes of other etiologies. Paroxysmal AF (PAF), a self-terminating recurrent form of cardiac arrhythmia that comprises between 25% and 62% of AF cases, may present as a brief single episode of arrhythmia or as clusters of abnormal rhythm of variable duration, sometimes evolving into a more persistent or permanent form. The self-terminating nature of PAF may lead to its underdiagnosis and consequent use of less effective treatment strategies (aspirin instead of oral anticoagulation) in poststroke patients.

To address the underdiagnosis of PAF in patients with ischemic stroke and TIA, several treatment guidelines have singled out the identification of PAF as an important goal after a stroke/TIA. The diagnosis of PAF, however, poses a challenge. Several features of AF (such as its brief duration, episodic frequency, and asymptomatic presentations) make its detection difficult and elusive to bedside screening measures, such as pulse monitoring and routine ECGs. To date, several studies have explored the use of prolonged noninvasive and invasive cardiac monitoring devices to identify AF but with variable success. After detection of AF, a cardioembolic mechanism is often inferred and anticoagulation occasionally prescribed for secondary stroke prevention. The routine use of cardiac monitoring to identify patients with PAF who will benefit from anticoagulation has been reported to be cost-effective.

In this review, we provide an overview of the different methods of cardiac monitoring, summarize studies that investigated the incidence of PAF after stroke, and highlight gaps in our understanding of the pathogenic and prognostic significance of AF detected on extended cardiac monitoring after a stroke or TIA.

The Spectrum of Atrial Tachyarrhythmias and Stroke Risks

Atrial tachyarrhythmias are heterogeneous, with etiologies that include rapidly discharging foci (most often in the pulmonary veins), microreentry, macroreentry, and automatic modulation of the atria, all of which occur in atria with varying degrees of structural abnormality. Because the surface ECG is acquired by recording from sites removed from the atria, it is an integrative recording that “summarizes” the degree of uniformity of atrial activation. Thus, some arrhythmias that may be classified as AF on the surface ECG may have some degree of organization regionally within the atrial myocardium. During AF, intracardiac recordings demonstrate wide regional variation, with complex fractionated electrograms and organized electrograms temporally coexisting. The relationship between atrial arrhythmia rate and complexity and thromboembolic risk is not well established.

Whereas some studies suggest that the stroke risk with atrial flutter (an organized, macroreentrant arrhythmia) is similar to that of AF, others suggest a continuum of stroke risk that increases with greater atrial rate and disorganization. The putative mechanisms of thromboembolism in AF include development of mechanical dysfunction and a proinflammatory and procoagulant state, with resultant thrombus formation in the complex, pectinate-rich structure of the left atrial appendage (LAA) (Figure 1), although the possibility that AF is merely a marker for the presence of stroke risk factors exists. Moreover, the LAA demonstrates great interindividual morphological heterogeneity. Whether this anatomic variability affects the risk of thromboembolism associated with atrial tachyarrhythmias is not known.

Evidence exists to indicate that the duration of an atrial tachyarrhythmia predicts its thromboembolic risk. Conversion of AF to sinus rhythm results in transient mechanical dysfunction of the LAA, the duration of which is a function of the length of the antecedent AF episode. Thus, although incompletely defined, factors that may play a role in thromboembolism in AF include the rate and duration of the atrial tachyarrhythmia, LAA morphology, and the presence of established risk factors (advanced age, heart failure, diabetes mellitus, hypertension, and previous TIA or stroke) (Figure 2). However, the minimum atrial rate and duration that are thrombogenic are not known. Current guidelines recommend anticoagulation for nonrheumatic AF on the basis of the presence of clinical risk factors, without regard to whether the AF is paroxysmal or permanent; furthermore, they propose...
treatment of atrial flutter and AF in an identical manner with regard to anticoagulation (class I, level of evidence C). For cardioversion, anticoagulation is recommended for episodes lasting >48 hours, although evidence to support this strategy is lacking. AF ablation guidelines suggest considering any episode lasting at least 30 seconds as a recurrence.

Importantly, the data available to inform current guidelines were compiled with the use of surface ECG recordings of limited temporal duration. The means of acquiring an ECG recording, whether by surface, subcutaneous, or intracardiac electrodes, determines the duration of monitoring and the sensitivity and specificity for the detection of atrial tachyarrhythmias of various atrial and ventricular rates and durations. These are described in detail below. It is likely that information obtained with the use of newer recording technologies will lead to revision of existing guidelines.

Noninvasive and Invasive Detection Methods
Since the discovery by Dr Norman Holter in the early 1960s of a method to record, store, and display cardiac electric waves,26 cardiac devices have become available to detect PAF, distinguish it from other arrhythmias, and monitor its response to antiarrhythmic treatments.27 With improvements in design and technology, newer devices are generally easy to wear, can be hidden under most clothing, and allow monitoring of patients for prolonged periods. Data are subsequently stored, uploaded, and analyzed automatically. The advent of implantable devices afforded the possibility of prolonged (even for years) continuous monitoring and direct myocardial recordings. AF detection devices are thus divided into 3 categories: (1) surface ECG systems; (2) subcutaneous recording systems; and (3) intracardiac recording systems (Table 1 and Figure 3).

Table 1. Different Methods of Cardiac Monitoring

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous hospital telemetry</td>
<td>• Accurate diagnosis</td>
<td>• Requires inpatient monitoring</td>
</tr>
<tr>
<td></td>
<td>• Detects asymptomatic events</td>
<td>• Expensive</td>
</tr>
<tr>
<td></td>
<td>• Detects asymptomatic events</td>
<td>• Restricts patient movement</td>
</tr>
<tr>
<td>Ambulatory ECG (Holter)</td>
<td>• Easy to use</td>
<td>• Short monitoring period</td>
</tr>
<tr>
<td></td>
<td>• Continuous recording</td>
<td>• Need for patient to keep symptom diary</td>
</tr>
<tr>
<td>Patient-triggered event recorder</td>
<td>• Longer monitoring periods</td>
<td>• Does not detect asymptomatic events</td>
</tr>
<tr>
<td></td>
<td>• Correlation of symptoms and rhythm</td>
<td>• Requires patient participation</td>
</tr>
<tr>
<td>Prolonged ambulatory ECG (mobile</td>
<td>• Continuous monitoring</td>
<td>• Costly</td>
</tr>
<tr>
<td>cardiovascular telemetry)</td>
<td>• Detects asymptomatic events</td>
<td>• Patient compliance, skin irritation</td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantable loop recorder</td>
<td>• Longer periods of follow-up</td>
<td>• Costly and invasive</td>
</tr>
<tr>
<td></td>
<td>• Internet-based data transmission</td>
<td>• False-positive and false-negative detections</td>
</tr>
<tr>
<td>Pacemakers and defibrillators</td>
<td>• Detects asymptomatic events</td>
<td>• Costly and invasive</td>
</tr>
<tr>
<td></td>
<td>• Offers therapy</td>
<td>• Great risk of complications</td>
</tr>
</tbody>
</table>

Surface Recording Systems
The ambulatory ECG (Holter) continuously records an ECG signal for 24 to 48 hours, although at some centers recordings of up to 7 days are available.28 It is battery operated and records 2 to 3 different leads. Versions that permit recording

Figure 1. Human atria, with ventricles removed. Note that the left atrium, which embryologically derives from venous tissues, has a smooth endocardium. The exception is the left atrial appendage (LAA), which has a complex structure that includes pectinates and small cul-de-sacs that allow blood stasis and thrombosis in the absence of mechanical contraction. There is a spectrum of atrial rhythmic disorganization ranging from atrial tachycardia and atrial flutter to atrial fibrillation. Some evidence suggests that the more rapid the atrial rhythm and the longer its duration, the greater is the potential for LAA thrombus formation, although support for this hypothesis is incomplete. Image courtesy of Dr William Edwards, Mayo Clinic.

Figure 2. Hypothesized interplay between atrial arrhythmia type and stroke risks. This concept plot displays relationships and is proposed as a means for understanding stroke risk in patients with atrial tachyarrhythmias. Note that if stroke risk factors are absent (front row in plot), the risk of stroke is low, irrespective of the degree of atrial rhythm disorganization or duration. Thus, patients with lone atrial fibrillation (< age 65 years and no other risk factors) are at low risk for thromboembolism. However, once risk factors are present, the longer the duration of arrhythmia and the greater the atrial rate (ie, flutter vs fibrillation), the greater is the risk. It is conceivable that individual left atrial appendage anatomy also affects stroke risk, but this has not been studied systematically.
up to 12 leads are available. Although more cumbersome, these permit characterization of premature ventricular complex morphology in patients who are potential ablation candidates; the benefit in atrial arrhythmia patients is less clear. Modern devices record data onto electronic media that are then analyzed with the help of software to identify rhythm abnormalities. Many recorders include patient-activated event markers as well as time markers to allow an increased correlation between symptoms and rhythm abnormalities.29 Tracings are overread by cardiologists, and Holter recordings are thus considered the gold standard. The greatest limitation is the recording period, typically 1 to 2 days.

In contrast, event recorders are used for prolonged time periods (4 to 6 weeks), with episodic recordings triggered by the patient. These devices may be worn continuously or applied only at the time of recording. Continuously worn devices record the ECG into a memory buffer loop, which is “frozen” when activated by the patient and permits capture of the ECG for several minutes before and after activation. Alternatively, a credit card–sized monitor that is applied to the chest wall at the time of symptoms of arrhythmia is also available. These generally require a symptomatic arrhythmia lasting at least 3 minutes to allow time for application of the device to the chest. Once a rhythm is recorded, the monitors transmit recordings by telephone by converting ECG data to audio signals. The audio signals are received at a central station that reconstructs the electric signal into a conventional ECG recording for interpretation.29 Newer forms of transmission (wireless, Internet based) are emerging. Event monitoring necessarily only captures symptomatic events, unless patients are instructed to transmit periodic rhythm samples. Patient compliance is required. Event recorders are useful for symptomatic patients and typically tolerated up to 4 weeks in motivated patients. Rhythm strips are overread by technicians and/or caregivers.

Mobile cardiac outpatient telemetry systems provide home-based, nearly continuous real-time monitoring of symptomatic...
ic and asymptomatic arrhythmias. Patients wear a small transmitting pendant that is connected to 3 ECG electrodes. The pendant transmits real-time ECG data to a cell phone–sized monitor that analyzes the rhythm. Any detected arrhythmias are transmitted via the cellular network to a laboratory where technicians read the episodes. Arrhythmias trigger immediate alerts on the basis of predetermined physician-set monitoring thresholds and response parameters. Patients may also activate the monitor to report symptoms. If a patient travels outside of the cell network, data are stored and transmitted when back in range. Monitoring is performed for 7 to 21 days, and patients remove and apply electrodes themselves. Newer devices composed of a “band aid” that records and transmits the ECG to a cell phone, which then analyzes and transmits the data to a back-end processor for human and/or computer processing, are currently under development and in early human trials.

As monitoring duration is lengthened, the burden of data for review increases, and automated algorithms to identify arrhythmias are increasingly deployed. Limitations of analysis of skin (and subcutaneous) recordings include the relatively small amplitude of atrial signals compared with ventricular signals and false-positives generated by myopotential and motion artifact. Published independent validation of many of these systems is limited.

The CardioNet mobile cardiac outpatient telemetry system (Conshohocken, PA) uses nonlinear statistics in a proprietary algorithm that analyzes R-R interval variability, QRS morphology, and P-wave presence to screen for AF. When tested against a standardized database of recorded and cataloged rhythms, the episode sensitivity and positive predictive values are 81% and 88%, respectively; with episodes of at least 30 seconds, the reported sensitivity and positive predictive values are 100% and 100% (Anna McNamara, Cardionet, written communication). In all noninvasive systems, real-world limitations include loss of signal because of inappropriate system use, myopotentials, artifact, and noncompliance. Thus, recording times are significantly extended beyond those available with standard Holter recordings but at the cost of noncontinuous recordings and loss of summary statistics (eg, premature ventricular contraction count). The rate of false-positives reported to clinicians is low because tracings are overread by technicians who prepare the reports that are then sent to the treating caregiver; the rate of false-negatives in clinical use is not currently known.

**Subcutaneous Recording Systems**

It is well established that the longer a patient is monitored, the greater is the likelihood of detecting symptomatic and asymptomatic AF. Implantable loop recorders are small (typically 6 cm by 2 cm by 0.8 cm) devices implanted subcutaneously to overcome the limitations of skin irritation and patient compliance to allow very prolonged recording periods. They automatically record tachyarrhythmias and bradyarrhythmias with physician-programmable parameters or when a patient triggers a recording with a wireless activator. A dedicated AF detection algorithm analyzes the variability in the difference between consecutive R-R intervals (ΔR-R[i] versus ΔR-R[i−1]). It analyzes irregularity to distinguish sinus rhythm (minor variations related to ectopy and sinus arrhythmia) from AF (uncorrelated irregularity). The duration and number of recordings are programmable, with current devices capable of recording up to 50 minutes of ECG. Data can be transmitted over the telephone or wirelessly with appropriate equipment to the Internet for Web-based physician review. The implant may be left in place up to 3 years and can be explanted once a diagnosis is made or the battery life has ended. Automatic triggers and the lack of external electrodes minimize the need for patient compliance to capture an event. In a study in which 247 patients received an implantable loop recorder (Reveal XT, Medtronic, Minneapolis, MN) with an automated algorithm and underwent simultaneous Holter recording for validation, the sensitivity, specificity, positive predictive value, and negative predictive value for identifying patients with any AF were 96.1%, 85.4%, 79.3%, and 97.4%, respectively. False-positives were recorded in 14.5% of patients because of premature atrial or ventricular complexes, myopotential oversensing, sinus arrhythmia, or undersensing of R waves, highlighting the importance of human overreading of automatically detected episodes. Episodes had to be at least 2 minutes in duration to permit detection, resulting in missed AF in 3.9% of patients. Considering episodes of longer duration (>6 minutes as opposed to 2 minutes) increases the positive predictive value from 73% to 80%.

**Intracardiac Recording Systems**

Dual-chamber pacemakers and implantable cardioverter-defibrillators include an atrial lead that permits direct recording of atrial electrograms (Figure 3). If the atrial rate exceeds a programmable value for a defined number of complexes, an atrial tachyarrhythmia is declared. Thus, in contrast to surface and subcutaneous systems, dual-chamber cardiac implantable electronic devices detect atrial tachyarrhythmias with a regular ventricular response, even if the ventricular rate is in the normal range. Importantly, single-chamber pacemakers generally do not detect atrial arrhythmias, and single-chamber implantable cardioverter-defibrillators only detect them if the ventricular rate exceeds the ventricular tachycardia detection rate. At that point, R-R interval variability is assessed. Thus, for reliable detection of atrial arrhythmias, dual-chamber systems are used.

Current-generation devices automatically record intracardiac electrograms for later review when arrhythmias are detected. The sensitivity for detection ranges from 57% to 98.1%, and the specificity ranges from 85.4% to 100%. Many of the arrhythmias may not be true AF but rather atrial tachycardias or atrial flutters with rates that exceed the programmable recording threshold. These are therefore referred to as atrial high-rate episodes. Manual overreading of recorded episodes is important because far-field R wave oversensing (Figure 4) and, less commonly, lead fracture or external electromagnetic signals may also trigger event capture. Because of intermittent undersensing, a single prolonged episode may be recorded as multiple shorter episodes so that the overall arrhythmia burden may be more reliable than number of episodes. Cardiac implantable electronic device batteries last 5 to 12 years, depending on the device type and therapy delivered.
Detecting Paroxysmal Atrial Fibrillation in Stroke Patients

Brief and predominantly asymptomatic presentations of AF (often referred to as occult PAF) may remain undetected by traditional methods of arrhythmia screening. Subsequent to earlier reviews in 2000 and 2007, numerous studies have been published that assess the use of cardiac monitoring devices to detect PAF in stroke patients. The incidence of new AF varies widely depending on the choice of cardiac monitoring devices, recruitment criteria of the study population, stroke characteristics, interval of monitoring from stroke onset, and duration of cardiac monitoring.

We performed a systematic review of studies that assessed the incidence of newly diagnosed PAF after stroke. For inclusion, studies were required to fulfill the following criteria: (1) consecutive recruitment of stroke or TIA subjects, (2) cardiac monitoring to detect AF for a minimum duration of 12 hours; and (3) detection of new AF with the use of either a noninvasive or invasive cardiac monitoring device. We identified 19 studies (6 prospective and 13 retrospective) that assessed the ability of cardiac monitoring devices to identify AF in consecutive patients after ischemic stroke, TIA, or both (Tables 2 and 3). The methods of cardiac monitoring in these studies were ambulatory ECG, continuous inpatient ECG, combined use of continuous and ambulatory ECG monitoring, automatic event recorder, and implantable loop recorder. Studies varied in their recruitment of subjects for cardiac monitoring. Some studies included subjects on the basis of clinical suspicion of embolic stroke, older age, or unknown stroke mechanism despite extensive investigations (cryptogenic strokes). In some studies, subjects were selected after additional screening for arrhythmia before prolonged cardiac monitoring. The duration of cardiac monitoring also differed significantly across studies, from 24 hours to as long as 14 months.

Detection of New Atrial Fibrillation

To determine the incidence of AF in this population, we considered the number of new cases of AF detected with the use of cardiac monitoring devices. Patients with AF diag-

Table 2. Detection of New-Onset Atrial Fibrillation in Unselected Populations of Stroke and Transient Ischemic Attack Patients

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study Population</th>
<th>Mean Age, y</th>
<th>Detection Methods</th>
<th>Eligible Patients After Excluding Established AF, n</th>
<th>Patients Diagnosed With New AF, n</th>
<th>Detection Rate of New AF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shafqat et al, 2004</td>
<td>Stroke</td>
<td>67</td>
<td>Ambulatory ECG (24 h)</td>
<td>210</td>
<td>5</td>
<td>2.4</td>
</tr>
<tr>
<td>Yu et al, 2009</td>
<td>Stroke</td>
<td>75</td>
<td>Ambulatory ECG (24 h)</td>
<td>96</td>
<td>9</td>
<td>9.4</td>
</tr>
<tr>
<td>Douen et al, 2008</td>
<td>Stroke</td>
<td>NM</td>
<td>Inpatient serial ECG</td>
<td>144</td>
<td>20</td>
<td>13.9</td>
</tr>
<tr>
<td>Koudstaal et al, 1986</td>
<td>TIA</td>
<td>61</td>
<td>Ambulatory ECG (24 h)</td>
<td>96</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Shaer et al, 2004</td>
<td>Stroke/TIA</td>
<td>67</td>
<td>Ambulatory ECG (24 h)</td>
<td>404</td>
<td>9</td>
<td>2.2</td>
</tr>
<tr>
<td>Alhadramy et al, 2010</td>
<td>Stroke/TIA</td>
<td>65</td>
<td>Ambulatory ECG (24 h)</td>
<td>413</td>
<td>11</td>
<td>2.7</td>
</tr>
<tr>
<td>Vivanco Hidalgo et al, 2009</td>
<td>Stroke/TIA</td>
<td>79</td>
<td>Inpatient continuous ECG (5 d)</td>
<td>465</td>
<td>16</td>
<td>3.4</td>
</tr>
<tr>
<td>Sposato et al, 2011</td>
<td>Stroke/TIA</td>
<td>67</td>
<td>Inpatient continuous ECG (48 h)</td>
<td>155</td>
<td>21</td>
<td>13.5</td>
</tr>
<tr>
<td>Rem et al, 1985</td>
<td>Stroke/TIA</td>
<td>66</td>
<td>Inpatient continuous ECG (48 h)</td>
<td>171</td>
<td>6</td>
<td>3.5</td>
</tr>
<tr>
<td>Stahrenberg et al, 2010</td>
<td>Stroke/TIA</td>
<td>68</td>
<td>Ambulatory ECG (7 d)</td>
<td>220</td>
<td>28</td>
<td>12.7</td>
</tr>
<tr>
<td>Lazaro et al, 2011</td>
<td>Stroke/TIA</td>
<td>63</td>
<td>Inpatient continuous ECG (48 h)</td>
<td>133</td>
<td>8</td>
<td>6.0</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td>2507</td>
<td>134</td>
<td>5.3</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; TIA, transient ischemic attack; and NM, not mentioned.
Table 3. Detection of New-Onset Atrial Fibrillation in Selected Populations of Stroke and Transient Ischemic Attack Patients

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study Population</th>
<th>Mean Age, y</th>
<th>Method of Patient Selection</th>
<th>Detection Methods</th>
<th>Eligible Patients After Excluding Established AF, n</th>
<th>Patients Diagnosed With New AF, n</th>
<th>Detection Rate of New AF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuchert et al, 1999</td>
<td>Stroke</td>
<td>61</td>
<td>Suspected embolic etiology</td>
<td>Ambulatory ECG (72 h)</td>
<td>82</td>
<td>4</td>
<td>4.9</td>
</tr>
<tr>
<td>Dion et al, 2010</td>
<td>Stroke</td>
<td>49</td>
<td>Cryptogenic stroke + negative 24-h ECG</td>
<td>Implantable loop recorder (14.5 mo)</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Jabaudon et al, 2004</td>
<td>Stroke/TIA</td>
<td>67</td>
<td>Negative 24-h ECG</td>
<td>Ambulatory ECG (7 d)</td>
<td>88</td>
<td>5</td>
<td>5.7</td>
</tr>
<tr>
<td>Rizos et al, 2010</td>
<td>Stroke/TIA</td>
<td>72</td>
<td>Age &gt;60 y</td>
<td>Inpatient continuous ECG (48 h) + ambulatory ECG (24 h)</td>
<td>136</td>
<td>29</td>
<td>21.3</td>
</tr>
<tr>
<td>Gaillard et al, 2010</td>
<td>Stroke/TIA</td>
<td>64</td>
<td>Negative 24-h ECG</td>
<td>Ambulatory ECG (transtelephonic) (30 d)</td>
<td>98</td>
<td>9</td>
<td>9.2</td>
</tr>
<tr>
<td>Tayal et al, 2008</td>
<td>Stroke/TIA</td>
<td>66</td>
<td>Negative 24-h ECG</td>
<td>Ambulatory ECG (MCOT) (21 d)</td>
<td>56</td>
<td>3</td>
<td>5.3*</td>
</tr>
<tr>
<td>Elijovich et al, 2009</td>
<td>Stroke/TIA</td>
<td>68</td>
<td>Cryptogenic only</td>
<td>Automatic event recorder (30 d)</td>
<td>20</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Barthelemy et al, 2003</td>
<td>Stroke/TIA</td>
<td>64</td>
<td>Cryptogenic stroke + negative 24-h ECG</td>
<td>Automatic event recorder (4 d)</td>
<td>28</td>
<td>4</td>
<td>14.3</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>532</td>
<td>58</td>
<td>10.9</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; TIA, transient ischemic attack; and MCOT, mobile cardiac outpatient telemetry.

*These rates of detection correspond to episodes of paroxysmal AF lasting >30 seconds. In addition, there was a 23% detection rate of paroxysmal AF episodes lasting <30 seconds.

nosed before their hospitalization or during routine inpatient screening were excluded from this analysis. Relevant data were abstracted from these studies by 2 investigators (R.C.S.S. and A.A.R.) and are summarized in Tables 2 and 3. A total of 3039 subjects (mean age, 66 years; 62% male gender) were included in this analysis. The average incidence of new AF in these studies was 6.3%, the highest incidence was in patients older than 60 years evaluated with continuous inpatient ECG and 24-hour Holter monitoring (21.3%),44 and the lowest incidence was detected in younger cryptogenic stroke patients monitored with an implantable loop recorder.45

Patient Selection

To determine the impact of patient selection on the detection yield of AF, we divided studies into 2 groups: an unselected population of stroke/TIA patients (11 studies; Table 2) and a population selected on the basis of age, stroke etiology, and prescreening for cardiac arrhythmias (8 studies; Table 3). The average incidence of new diagnosis of AF in an unselected population was 5.3%, whereas the average incidence in the selected population was 10.9%. When selection criteria were applied, the mean detection yield of AF with ambulatory ECG was 6.4% (range, 5.3% to 9.0%); with combined use of continuous inpatient and ambulatory ECG, it was 21.3%; and with automatic event recorder, it was 16.7% (range, 14.3% to 20.0%). Despite a longer period of monitoring (14.5 months), the implantable loop recorder did not detect significant cardiac abnormalities in younger stroke patients with fewer AF risk factors.45

Stroke Characteristics

Several studies compared the incidence of AF according to stroke subtypes, locations, and severity. A higher incidence of AF was observed in patients with cryptogenic stroke compared with those with large atherothrombotic and lacunar strokes in one study41 but not in another.58 Subsequent studies restricted to patients with cryptogenic stroke found an incidence of AF ranging between 14.3% and 27.3%.50,57,58 In younger patients with cryptogenic stroke, however, the use of implantable loop recorders was not able to detect new cases of AF.45 Among patients with suspected embolic strokes, the incidence of AF was 6% in a study that used a 72-hour ambulatory ECG monitoring device.44 The wide range of reported incidences in these patients may arise from uncertainties concerning the definition of cryptogenic stroke. The term cryptogenic stroke usually refers to strokes with no clearly definable cause despite extensive workup.60 The yield from these investigations to elucidate the etiology of stroke may vary depending on the practice of centers managing stroke patients, timing of investigations (because some causes may be reversible, such as cardiac thrombus and vegetations), and lack of expertise or manpower to routinely perform more specialized investigations such as transesophageal echocardiogram and transcranial Doppler study. In the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) study, a randomized prospective study that compares standard arrhythmia monitoring (control arm) and implantation of a subcutaneous cardiac monitor (Reveal XT; Medtronic, Inc, Minneapolis, MN) (continuous monitoring arm) for AF detection, a stroke/TIA is considered to be cryptogenic if no possible cause can be determined according to the standard protocol of the participating center.61

Because an embolus from the heart may preferentially lodge in the anterior circulation or break up and lead to multiple ischemic foci, studies assessing infarcted territory and its association with AF have been performed. In 1 study, the incidence of AF was higher in patients with anterior circulation territory infarctions than in those with lacunar stroke (68% versus 0%).53 Patients with AF had severe neurological deficits (National Institutes of Health Stroke Scale >10) more often than those without AF (n=5, 22.7%).
versus n=4, 3.1%; P=0.003).53 In other studies, brain imaging parameters such as infarct size,50 number of infarcts,48 and stroke locations55,59 were identified as significant predictors of AF detection after acute stroke. A combination of clinical and radiological features (comprising embolic infarct pattern, age >65 years, and preexistent coronary artery disease) has also been associated with a higher incidence of AF.59

**Timing and Duration of Cardiac Monitoring**

Limited data are available on the optimal time and duration of monitoring. Seven studies reported the interval between stroke onset and the timing of cardiac monitoring, which ranged from 72 hours to 3 months after the stroke.44–46,50,55,56,58 The duration of cardiac monitoring was reported in 13 studies and ranged from 22 hours to 14 months.41–44,45,47–49,53–59 Regardless of the detection method used, studies evaluating earlier monitoring reported a higher incidence of AF than those in which monitoring was pursued later.54 Similarly, studies that monitored patients for a longer period identified a higher incidence of AF.50,52,55,57,58

**Comparison Between Different Detection Methods**

Concerns have been raised about the low agreement between different cardiac monitoring methods to detect AF. One study suggested superiority of ambulatory ECG monitoring over continuous inpatient ECG,59 whereas another claimed superiority of continuous inpatient ECG over ambulatory ECG monitoring.54 In certain studies, ambulatory ECG actually failed to corroborate the detection of AF on 12-lead and serial ECGs.41,43 These differences highlight the practical difficulties faced by investigators and neurologists to capture the intermittent and periodic bursts of AF, which may vary depending on the device used and the timing of cardiac monitoring.

**Significance of Paroxysmal Atrial Fibrillation Detected After Stroke**

AF may lead to stroke due to diminished blood flow within the complex anatomy of the trabeculated LAA, promoting thrombus formation by associated inflammation and activation of thromboxane and other rheostatic factors.17 Whether PAF (with intervening sinus rhythm that may promote thrombus dislodgement via LAA contraction) leads to an elevated risk or lower risk (because of less time in fibrillation) is poorly understood. In patients with PAF determined by standard surface ECG tracings, the risk of stroke in patients with PAF is similar to that observed with chronic and persistent forms of AF.56 and current guidelines recommend treating PAF on the basis of the concomitant stroke risk factors in a manner identical to persistent forms with regard to stroke prophylaxis.7-8 However, new technology now allows identification of very brief episodes of PAF, the significance of which is uncertain. It is not known, for example, whether patients with PAF included in previous trials could represent a selected population with high AF burden (sufficient to be detected by routine ECG) resulting in a stroke risk comparable to that of patients with chronic AF.63,64 Whether the very brief episodes of PAF detected by prolonged rhythm monitoring are associated with a similar stroke risk remains to be established. Still, growing data support an independent association between these episodes of PAF and history of cerebral ischemia or future risk of stroke. The brief episodes of PAF could directly contribute to atrial thrombus formation or represent markers of longer episodes of PAF that occur outside of the monitoring period.

Studies of patients with implanted devices provide emerging evidence that very brief arrhythmia episodes are associated with stroke risk. In the Mode Selection Trial (MOST), atrial high-rate episodes lasting at least 5 minutes predicted a higher incidence of the composite outcome of death and nonfatal stroke.65 In the Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics (TRENDS), episodes of atrial tachyarrhythmia/AF were detected by a pacemaker or implantable cardioverter-defibrillator in 28% of patients with previous thromboembolic events and an indication for implantation of the device.66 In this cohort, a threshold of atrial tachyarrhythmia/AF burden >5.5 hours on any of the preceding 30 days of monitoring was associated with an annualized thromboembolic rate of 2.4% (95% confidence interval, 1.2% to 4.5%).67 The rate of thromboembolic events was low compared with that in patients with AF diagnosed by traditional modalities and similar CHAD2 scores, but the risk was still doubled in patients with an atrial tachyarrhythmia/AF burden >5.5 hours compared with those with no atrial tachyarrhythmia/AF (P=0.06).67

Evidence for the importance of very brief episodes of atrial tachyarrhythmias comes from the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) (S.J. Connolly, MD, unpublished data, 2010). Hypertensive patients aged ≥65 years with a clinical indication for a dual-chamber pacemaker or implantable cardioverter-defibrillator and no history of AF were enrolled (n=2580). Atrial high-rate episodes were defined as an atrial rate >190 bpm lasting >6 minutes and were adjudicated by expert clinicians. Patients were prospectively followed for stroke or thromboembolism for a mean of 2.8 years, and the cumulative rate of vitamin K antagonists was <2% per year. Remarkably, despite the lack of a clinical history of AF, 36% of patients had an atrial high-rate episode during the study. The presence of an atrial high-rate episode conferred a relative risk of 2.49 (P<0.007) for subsequent ischemic stroke or systemic embolism. The study has been presented but not yet published; additional insights are certain to emerge once the analysis of these data is completed.

Another study showed that brief bursts of PAF detected by Holter (mean monitoring time 22.6 hours; bursts often <30 seconds) were associated with the presence of acute and chronic brain infarcts on brain imaging, especially cortical lesions consistent with embolism.48 High detection rates have been reported with the use of 21-day monitoring with mobile cardiac outpatient telemetry, but most of these episodes are very brief. In 1 study, 5.3% of cryptogenic stroke patients had episodes of PAF lasting >30 seconds, and 23% had episodes lasting <30 seconds.56

When patients with previous stroke are monitored, it is pertinent to ask if the observed arrhythmia could be a consequence (rather than a cause) of cerebral ischemia. ECG
abnormalities, including atrial arrhythmias, have been reported in patients with no underlying cardiac disease.\textsuperscript{51,68} There is considerable evidence indicating that the insulin cortex has a substantial role in the regulation of cardiac rate and rhythm and supporting the concept that insular infarctions can be arrhythmogenic.\textsuperscript{69} Studies reporting a significantly higher incidence of atrial tachyarrhythmias immediately after an ischemic stroke,\textsuperscript{50,54} especially in patients with total anterior circulation infarction,\textsuperscript{53} support the hypothesis of a cerebrogenic source of the cardiac arrhythmia. It remains to be determined whether brief episodes of PAF can be a transient phenomenon after an insular stroke. Moreover, pooled data from the Stroke Prevention in Atrial Fibrillation (SPAF) studies indicate that $\approx30\%$ of strokes in AF patients are noncardioembolic in etiology.\textsuperscript{70}

### When Should Paroxysmal Atrial Fibrillation Be Treated?

Once PAF is identified by traditional modalities, oral anticoagulant therapy is indicated to prevent stroke recurrence.\textsuperscript{7,8} However, the optimal management of very brief episodes detected by newer technologies is not known. In some studies, the detection of AF with prolonged monitoring devices after a stroke led to a change in the choice of antithrombotic treatment.\textsuperscript{43,47,50,55,57,59} In 1 study, oral anticoagulation was started in 28.6\% of patients with a new diagnosis of AF detected by ambulatory 7-day ECG monitoring and in all 5 patients with AF detected by loop event recorder.\textsuperscript{53} However, caution should be exercised when one extrapolates the potential benefits of anticoagulation to stroke patients with PAF detected by prolonged monitoring with the use of novel devices. At present, there are no data from randomized controlled trials to guide the appropriate treatment of brief episodes of PAF newly detected by prolonged rhythm monitoring after a stroke or TIA. Such trials are needed.

### Conclusions

Cardiac monitoring may play an important role in the surveillance of cardiac arrhythmias after stroke/TIAs. With wider use and improved methods of cardiac monitoring, the incidence of PAF is expected to increase in the near future. However, several clinical questions regarding cardiac monitoring must be addressed, including the following: What are the optimal timing and duration of cardiac monitoring? Who are the best candidates for prolonged cardiac monitoring? What is the pathological and prognostic significance of brief symptomatic and asymptomatic PAF detected after stroke/TIAs? Finally, what is the efficacy of anticoagulation to prevent stroke recurrence in these patients? Future studies should include information on demographics, interval from time of stroke, stroke characteristics (subtypes and severity), cerebrovascular risk factors, duration of monitoring, measure of AF burden, and, ideally, longer-term incidence of recurrent cerebrovascular events in patients with these arrhythmias. It is not clear whether data from previous trials, derived from patients with predominantly chronic and persistent AF, can be safely extrapolated to support the practice of prescribing anticoagulation for these patients. Until data on the yield of prolonged ambulatory monitoring and the optimal treatment when AF is detected by this method are available, we believe that such monitoring should be reserved for selected patients with cryptogenic stroke and cerebrovascular events suspicious for embolism.

### Disclosures

Drs Friedman and Rabinstein have received an unrestricted educational grant from CardioNet to study the incidence of PAF in ischemic stroke patients. Dr Seet has no conflict to report. Mayo Clinic and Dr Friedman have a financial interest in the development of a noninvasive remote monitoring platform that Mayo Clinic is developing with industry partners. The platform is not yet commercially available, and is not discussed in the present review article.

### References


Key Words: atrial fibrillation || rhythm monitoring || stroke || transient ischemic attack
Prolonged Rhythm Monitoring for the Detection of Occult Paroxysmal Atrial Fibrillation in Ischemic Stroke of Unknown Cause
Raymond C.S. Seet, Paul A. Friedman and Alejandro A. Rabinstein

Circulation. 2011;124:477-486
doi: 10.1161/CIRCULATIONAHA.111.029801
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/124/4/477

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/