Prolonged Cardiac Monitoring for Detection of Paroxysmal Atrial Fibrillation After Cerebral Ischemia

Alejandro A. Rabinstein, MD

Atrial fibrillation (AF) is a common arrhythmia, and its prevalence continues to rise with the aging of the population. It is the most frequent cause of ischemic stroke in elderly patients. Strokes from AF tend to be more severe and disabling. Consequently, the societal effect of AF-related strokes is large.

Despite advances in our understanding of stroke mechanisms, 20% to 30% of all strokes remain cryptogenic. Many of them have an embolic pattern on brain imaging and, therefore, an occult embolic source is suspected. Reported rates of cryptogenic stroke recurrence vary across cohorts but may be high. On the basis of current evidence, we found that patients with cryptogenic stroke or transient ischemic attack (TIA) are generally treated with antiplatelet therapy and control of vascular risk factors. Although this therapeutic strategy is adequate for arterial sources of embolism, it might be insufficient if a cause of cardiac embolism has been missed.

AF is often paroxysmal and asymptomatic. In fact, paroxysmal AF (PAF) may be more prevalent than persistent AF among patients with stroke. In a large study of consecutive patients with TIA or stroke, nearly two thirds of cases of AF were paroxysmal. PAF carries the same risk of stroke as persistent AF. Brief, asymptomatic episodes of PAF can be difficult to detect by conventional methods (ie, ECG, Holter monitoring of short duration, patient-activated loop recorders). Thus, occult PAF is a likely candidate to explain at least some cases of cryptogenic stroke or TIA. This is particularly important because oral anticoagulation might be indicated in these cases.

Recent technological advances have made it possible to monitor for PAF in the ambulatory setting for prolonged periods of time (weeks, months, and even years). These devices are extremely sensitive and can uncover brief and asymptomatic episodes of PAF. They can also provide information on the burden of PAF over the monitoring period (ie, total amount of time in AF determined by duration and frequency of PAF episodes). Yet, the optimal use of these diagnostic techniques and the therapeutic implications of the findings remain to be established.

This review summarizes the state of the evidence linking occult PAF with increased risk of stroke and discusses the value of prolonged ambulatory monitoring for PAF detection after cerebral ischemic events.
Methods for Prolonged Ambulatory Cardiac Rhythm Monitoring

This topic has been discussed in detail in recent review articles.10,16 Basically, methods of prolonged ambulatory monitoring for PAF can be divided into noninvasive and invasive (Table 1). Noninvasive methods rely on surface electrodes. Invasive methods can be subcutaneous or intracardiac. Automatic identification of rhythm abnormalities is necessary for reliable detection of PAF. Because these episodes are so often asymptomatic, patient-activated devices are much less useful. Automatic detection is achieved by the application of proprietary algorithms of ECG analysis that vary across devices. Over-reading of the pertinent tracings by a cardiologist is advisable.

Holter monitoring is sensitive and specific for PAF detection, but the duration of monitoring is relatively short (1–2 days in most practices). Automatically triggered, noninvasive loop recorders typically can be worn for longer periods but have small memory capacity, require active participation of the patient (when an autotriggered event occurs, the device emits an alert to the patient, who must then transmit the data telephonically), and provide information on the onset but not the offset of the episode, thus not allowing calculation of PAF burden. Ambulatory telemetry monitoring systems have a battery-powered sensor that can hold ≤59 minutes of ECG data. They can provide nearly real-time monitoring. With most systems, the sensor sends continuous ECG data to a handheld device, which in turn transmits the data to a central monitoring station without detected PAF, and few have reported information on the offset of the episode, thus not allowing calculation of PAF. Moreover, studies have had sufficient follow-up to determine reliably the rates of recurrent stroke/TIA in patients with and without detected PAF, and few have reported information

When cellular coverage is available. Ambulatory telemetry systems can detect PAF episodes as short as a few seconds. Limitations include lack of patient compliance (ie, not wearing the device)7 and myopotential and motion artifacts. The monitoring center can determine whether the patient is wearing the device and ascertain the quality of the recording.

Implantable loop recorders are small leadless devices implanted subcutaneously through a minimally invasive procedure that has been developed to overcome the limitations of patient compliance and skin irritation. These devices allow monitoring for ≤3 years and can be easily extracted at any time. They are MRI compatible. Tachyarrhythmias and bradyarrhythmias are automatically recorded based on programmable parameters, and current devices can store ≤59 minutes of ECG data. All information is transmitted wirelessly to the monitoring company and then becomes available for physician review via internet. Implantable loop recorders only detect episodes of arrhythmia ≥2 minutes.

Both dual-chamber pacemakers and implantable cardioverter-defibrillators are intracardiac devices that can be programmed to detect atrial tachyarrhythmias even if the ventricular response is regular and maintains a normal rate. Studies using these devices have grouped PAF, atrial flutter, and atrial tachycardia as atrial high-rate episodes.11,12,15 Current batteries may last >10 years. Of course, these permanent devices are primarily therapeutic and only indicated in patients with life-threatening arrhythmias.

Studies of Prolonged Ambulatory Monitoring for PAF Detection After Stroke/TIA

Published studies of prolonged ambulatory PAF monitoring after a cerebrovascular event are summarized in Table 2. These studies have examined different devices, durations of monitoring, and intervals from the stroke/TIA. Patient selection was variable as well, with most but not all focusing on cryptogenic cases. The definitions of cryptogenic stroke and PAF were not uniform across studies. The majority have been observational studies evaluating a single type of device. Because of the heterogeneity across studies and the lack of comparative trials among different devices, the rates of PAF detection are not strictly comparable. None of these studies have had sufficient follow-up to determine reliably the rates of recurrent stroke/TIA in patients with and without detected PAF, and few have reported information

Table 1. Main Characteristics of Available Methods for Prolonged Ambulatory Cardiac Rhythm Monitoring

<table>
<thead>
<tr>
<th>Device</th>
<th>Location</th>
<th>Duration</th>
<th>Minimal Threshold</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holter</td>
<td>Skin surface</td>
<td>Usually 1–2 d</td>
<td>Few seconds</td>
<td>Short duration</td>
</tr>
<tr>
<td>External loop recorder</td>
<td>Skin surface</td>
<td>≤30 d</td>
<td>Few seconds</td>
<td>Requires patient action</td>
</tr>
<tr>
<td>Ambulatory telemetry</td>
<td>Skin surface</td>
<td>≤30 d</td>
<td>Few seconds</td>
<td>Patient compliance, Skin irritation</td>
</tr>
<tr>
<td>Implantable loop recorder</td>
<td>Subcutaneous</td>
<td>≤3 y</td>
<td>2 min</td>
<td>Invasiveness (minimal), Does not detect PAF ≤2 min</td>
</tr>
<tr>
<td>Dual-chamber pacemaker and defibrillator</td>
<td>Intracardiac</td>
<td>Many years</td>
<td>Seconds</td>
<td>Only indicated for life-threatening arrhythmias</td>
</tr>
</tbody>
</table>

PAF indicates paroxysmal atrial fibrillation.
Table 2. Studies of Prolonged (>48 Hours) Ambulatory Cardiac Rhythm Monitoring in Patients With Stroke/TIA

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Patient Selection</th>
<th>Interval From CV Event</th>
<th>Definition of PAF</th>
<th>Type of Monitor</th>
<th>Duration</th>
<th>Diagnostic Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higgins et al18</td>
<td>100</td>
<td>Randomized trial</td>
<td>Any TIA or stroke without known AF</td>
<td>≤7 d</td>
<td>20 s for sustained &lt;20 s but 6 VC for nonsustained*</td>
<td>50 SP</td>
<td>7 d</td>
<td>4% SP</td>
</tr>
<tr>
<td>Rabinstein et al19</td>
<td>132</td>
<td>Case control</td>
<td>66 CS 66 SKC</td>
<td>≤90 d (28±20 d)</td>
<td>Any duration*</td>
<td>MCOT (all)</td>
<td>21 d</td>
<td>44% ELaR for PAF of any duration</td>
</tr>
<tr>
<td>Ritter et al20</td>
<td>60</td>
<td>Prospective cohort, comparative</td>
<td>CS</td>
<td>13 d (OR, 10–65)</td>
<td>30 s (2 min required for ILR detection)*</td>
<td>ILR plus initial 7-d Holter</td>
<td>ILR 382 d (OR, 89–670)</td>
<td>17% ILR</td>
</tr>
<tr>
<td>Etgen et al21</td>
<td>22</td>
<td>Prospective cohort</td>
<td>CS</td>
<td>Mostly within 10 d</td>
<td>6 min</td>
<td>ILR</td>
<td>365 d</td>
<td>27%</td>
</tr>
<tr>
<td>Cotter et al22</td>
<td>51</td>
<td>Prospective, cohort</td>
<td>CS</td>
<td>174±134 d</td>
<td>2 min*</td>
<td>ILR</td>
<td>Until detection ≤229±116 d</td>
<td>25.5%</td>
</tr>
<tr>
<td>Kamel et al17</td>
<td>40</td>
<td>Randomized trial</td>
<td>CS or CTIA</td>
<td>≤60 d (22±12 d)</td>
<td>30 s*</td>
<td>20 MCOT 20 routine follow-up</td>
<td>21 d</td>
<td>0% (36% had MCOT noncompliance)</td>
</tr>
<tr>
<td>Miller et al23</td>
<td>156</td>
<td>Retrospective cohort</td>
<td>Mostly CS or CTIA (24% were not cryptogenic)</td>
<td>≤180 d (33±36 d)</td>
<td>Any duration</td>
<td>MCOT</td>
<td>≤30 d</td>
<td>17.3%</td>
</tr>
<tr>
<td>Flint et al24</td>
<td>239</td>
<td>Prospective cohort</td>
<td>CS</td>
<td>29 d (17–50 d)</td>
<td>5 s*</td>
<td>aELR</td>
<td>≤30 d (24.5±9 d)</td>
<td>12.1%</td>
</tr>
<tr>
<td>Manina et al25</td>
<td>114</td>
<td>Prospective cohort</td>
<td>CS or CTIA</td>
<td>Up to 30 d</td>
<td>Any duration*</td>
<td>Holter</td>
<td>4 d</td>
<td>24.3%</td>
</tr>
<tr>
<td>Doliwa et al26</td>
<td>249</td>
<td>Prospective cohort</td>
<td>Any TIA or stroke without AF</td>
<td>≤14 d</td>
<td>10 s*</td>
<td>Serial ECG, patient activated</td>
<td>30 d</td>
<td>6%</td>
</tr>
<tr>
<td>Bhatt et al27</td>
<td>62</td>
<td>Retrospective cohort</td>
<td>CS or CTIA</td>
<td>29 d (16–48) after hospital discharge</td>
<td>30 s*</td>
<td>MCOT</td>
<td>≤28 d</td>
<td>24%</td>
</tr>
<tr>
<td>Stahrenberg et al28</td>
<td>224</td>
<td>Prospective cohort</td>
<td>Any TIA or stroke without AF</td>
<td>9.5 h (6R, 6–16 h)</td>
<td>Any duration*</td>
<td>Holter</td>
<td>7 d</td>
<td>12.5%</td>
</tr>
<tr>
<td>Guillard et al29</td>
<td>98</td>
<td>Retrospective cohort</td>
<td>Mostly CS or CTIA (16% were not cryptogenic)</td>
<td>≤180 d</td>
<td>32 s*</td>
<td>TTM with serial ECG (patient activated)</td>
<td>≤30–90 d</td>
<td>9.2%</td>
</tr>
<tr>
<td>Dion et al30</td>
<td>24</td>
<td>Prospective cohort</td>
<td>CS, age &lt;75 (mean age, 49±14 y)</td>
<td>Up 120 d</td>
<td>Any duration*</td>
<td>ILR</td>
<td>14.5 m</td>
<td>4.2%</td>
</tr>
<tr>
<td>Elijovich et al31</td>
<td>20</td>
<td>Retrospective cohort</td>
<td>CS or CTIA</td>
<td>NA</td>
<td>30 s*</td>
<td>aELR</td>
<td>≤30 d</td>
<td>20%</td>
</tr>
<tr>
<td>Tayal et al32</td>
<td>56</td>
<td>Retrospective cohort</td>
<td>CS or CTIA</td>
<td>≤90 d</td>
<td>Any duration</td>
<td>MCOT</td>
<td>≤21 d</td>
<td>23%</td>
</tr>
<tr>
<td>Jabaudon et al33</td>
<td>88</td>
<td>Prospective cohort</td>
<td>Any TIA or stroke (patients with remote PAF were not excluded)</td>
<td>Mean 55 d</td>
<td>NA</td>
<td>aELR</td>
<td>7 d</td>
<td>5.7%</td>
</tr>
<tr>
<td>Barthélémy et al34</td>
<td>60</td>
<td>Prospective cohort</td>
<td>Any TIA or stroke (including 28 with CS or CTIA)</td>
<td>10±2 d</td>
<td>30 s</td>
<td>aELR</td>
<td>4 d (70±31 h)</td>
<td>20% whole cohort</td>
</tr>
<tr>
<td>Schuchert et al35</td>
<td>82</td>
<td>Retrospective cohort</td>
<td>CS</td>
<td>≤14–21 d</td>
<td>1 min</td>
<td>Holter</td>
<td>3 d</td>
<td>14.3% CS/CTIA</td>
</tr>
</tbody>
</table>

aELRa indicates automatic external loop recorder, SP-AM; CS, cryptogenic stroke; CTIA, cryptogenic transient ischemic attack; ILR, implantable loop recorder; IQR, interquartile range; MCOT, mobile cardiac outpatient telemetry; NA, not available; PAF, paroxysmal atrial fibrillation; SP, standard practice; SKC, stroke of known cause; TIA, transient ischemic attack; TTM, transtelephonic ECG monitoring; and VC, ventricular cycles.

*Overread by cardiologists.
on the decision made by clinicians on anticoagulation once PAF was detected. Yet, the combined assessment of available studies provides useful insights.

The detection yield increases with the duration of monitoring, the sensitivity of the device, and the inclusiveness of the definition of PAF.36,37 Episodes of PAF lasting for only a few seconds predominated in studies using ambulatory telemetry monitoring.19,32 Yet these episodes would not have been captured by implantable loop recorders that only detect episodes of ≥2 minutes. The yield may also be higher with stricter patient selection (eg, stroke rather than TIA and cryptogenic rather than any mechanism) and when initiated sooner after the cerebrovascular event.10 The value of greater burden of PAF in predicting future stroke risk demonstrated in patients with intracardiac devices13,16 cannot be confirmed by these studies because they did not report on recurrent clinical events; however, it is likely that PAF burden represents a useful measure of stroke risk.36,37

Only 1 study was compared with rates of PAF detection in patients with cryptogenic stroke versus stroke of known causes.18 In this prospective study, PAF of any duration was detected by mobile outpatient telemetry monitoring not only in 25% of patients with cryptogenic stroke, but also in 14% of patients with stroke of known cause; the difference was not significant (P = 0.12). PAF was more common in the cryptogenic group among patients <65 years of age (22% versus 3%; P = 0.07), whereas detection rates were similar in older patients (27% in the cryptogenic group versus 25% in the group of stroke with known cause). These results indicate that occult PAF is common in patients with stroke in general and give us reason for pausing before assuming that PAF was the cause of a previous cryptogenic stroke when the arrhythmia is detected by these sensitive methods of prolonged ambulatory monitoring. In addition, it is possible that new PAF may be induced by the cerebral infarction, particularly when involving the insular region.38

The Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL AF) trial is a recently completed randomized, prospective study examining the value of long-term monitoring for AF detection in patients with recent (<60 days) cryptogenic stroke (including clinical TIA with infarction on brain imaging).39 It randomized 448 patients to continuous monitoring using a subcutaneous implantable recorder (Reveal XT; Medtronic Inc) or to standard arrhythmia monitoring. Patients had ≥12 months of follow-up. The primary outcome was the time to the first documented event of AF. Incidence of recurrent stroke or TIA was one of the secondary outcome measures. These results will be greatly informative to quantify the rate of detection of occult PAF in patients with cryptogenic stroke using highly sensitive, prolonged ambulatory monitoring. However, they will not answer the question of whether anticoagulation is beneficial in all patients who have PAF detected by prolonged monitoring.

These methods of prolonged ambulatory cardiac monitoring are expensive. There is scant evidence on the cost-effectiveness of prolonged monitoring, but 1 study suggested that 1-week ambulatory cardiac monitoring was cost-effective.40 Additional research on cost-effectiveness of longer monitoring with implantable devices is necessary.

**Best Candidates for Prolonged Monitoring**

Because of the high cost of prolonged monitoring, it is important to identify which patients are more likely to have occult PAF. Several risk factors have been reported (Table 3), and some risk-stratification scores have been proposed.22,41–47 Older age is the factor most consistently associated with higher risk of AF, and this risk increases with the accumulation of vascular risk factors and in patients with documented vascular disease. Thus, most patients with stroke already have some of the main risk factors for AF. Yet, findings on brain imaging (embolic pattern),41,42 ECG/Holter (frequent premature atrial complexes),22,29,43 and echocardiography (left atrial dilatation on transthoracic and perhaps reduced left atrial appendage ejection fraction on transesophageal echocardiogram) can help stratify the risk further.22,45–47

It is reasonable to restrict prolonged ambulatory cardiac rhythm monitoring to patients with stroke deemed cryptogenic after a comprehensive evaluation and an embolic pattern on brain imaging (multiterritorial or single cortical-subcortical infarctions). Monitoring should be initiated early after the cerebrovascular event to maximize the detection yield. Although older patients with stroke are more likely to have underlying PAF, this is the case regardless of whether the stroke is cryptogenic.19 Meanwhile, younger patients with occult PAF may be ideal candidates for anticoagulation. Thus, age should not be a deciding factor when considering prolonged monitoring. It is also reasonable to restrict prolonged monitoring to patients who are deemed to be safe candidates for oral anticoagulation if PAF is detected.

**Therapeutic Implications**

Most of what is known about the risk of stroke related to AF comes from studies that relied on conventional methods of AF diagnosis (ECG, bedside telemetry, 24–48-hour Holter monitoring). Chronic anticoagulation unquestionably reduces the frequency of ischemic stroke in patients with AF, including PAF, diagnosed by conventional methods,6,48 and adequate intensity of oral anticoagulation (ie, international normalized ratio ≥2 in patients taking warfarin) also reduces stroke severity and stroke-related mortality.49,50 The question

| Table 3. Risk Factors for Paroxysmal Atrial Fibrillation Detection |
|--------------------|--------------------------|
| Risk factor | Description |
| Older age | Documented vascular disease |
| Cryptogenic stroke/TIA | Vascular risk factors (higher CHADS2 or CHA2DS2-VASc score) |
| Documented vascular disease | Greater stroke severity |
| Vascular risk factors (higher CHADS2 or CHA2DS2-VASc score) | Frequent PACs on ECG or Holter |
| Greater stroke severity | Left atrial dilatation on TTE |
| Frequent PACs on ECG or Holter | Left atrial appendage dysfunction on TEE |
| Left atrial dilatation on TTE | Multiterritorial or single corticosubcortical DWI lesions |

DWI indicates diffusion-weighted imaging sequence on MRI; CHADS2, congestive heart failure, hypertension, age, diabetes, prior stroke/TIA; CHA2DS2-VASc, CHADS2, vascular disease, age, sex category; PACs, premature atrial complexes; TEE, transesophageal echocardiogram; TIA, transient ischemic attack; and TTE, transthoracic echocardiogram.
is whether this therapeutic benefit from anticoagulation extends to patients with occult PAF detected by prolonged ambulatory monitoring.

For patients with AF at large, the decision to anticoagulate is optimally made after balancing the risk of stroke and the risk of anticoagulation-associated hemorrhage. Scores have been reliably validated to quantify the weights on both sides of the balance, and they should be used in practice. The CHADS2 and CHA2DS2-VASc (CHA2DS2, vascular disease, age, sex category) are the 2 most commonly used scores for stroke risk stratification, whereas scores such as HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR [international normalized ratio], elderly, drugs/alcohol) and HEMORR2HAGES (hepatic/renal disease, ethanol abuse, malignancy, older age, reduced platelet count/function, rebellious risk, hypertension, anemia, genetic factors, excessive fall risk, stroke) predict the risk of hemorrhage. Calculating these scores before embarking on prolonged monitoring is advisable to ensure parsimonious use of this costly diagnostic modality.

The individual burden of occult PAF should probably be considered when deciding whether to anticoagulate because greater PAF burden has been associated with greater stroke risk. Yet, it remains unknown whether there is a minimum PAF burden threshold below which the risk of stroke does not justify anticoagulation. For instance, is a single episode of PAF lasting <30 seconds for a monitoring period of 3 weeks a sufficient indication for life-long anticoagulation?

Current Gaps and Future Directions

Available evidence supports considering prolonged ambulatory cardiac rhythm monitoring after a cryptogenic stroke or TIA in patients who may be good candidates for anticoagulation. However, there are still major gaps in our understanding of the role and implications of this type of monitoring. Are brief episodes of occult PAF detected by prolonged monitoring associated with a risk of stroke similar to that documented with AF diagnosed by traditional methods? Who should be monitored, when, and for how long? What is the optimal monitoring device? Are the results of monitoring useful to guide anticoagulation?

Future studies need to be specifically designed to answer these questions. They should determine the stroke risk associated with various degrees of PAF burden (including whether many brief episodes or less frequent longer episodes carry greater risk), the variation in stroke risk depending on the presence of concurrent vascular risk factors, and the optimal use of anticoagulation. One of the main concerns is that prescribing anticoagulation to every patient with PAF on prolonged monitoring could result in excessive treatment and unnecessary exposure to the risk of hemorrhage. Individualized management should be the objective. Current clinical practice is variable because of insufficient evidence to guide this decision. Trials of anticoagulation guided by prolonged ambulatory rhythm monitoring are necessary.

The Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk (IMPACT) study, which has completed recruitment (n=2718), is a multicenter, randomized trial designed to investigate whether anticoagulation guided by prolonged rhythm monitoring in patients with an implanted dual-chamber cardiac resynchronization therapy defibrillator can reduce the risk of stroke, systemic embolism, and major bleeding when compared with conventional clinical management. Patients in the prolonged monitoring arm start anticoagulation when an atrial high-rate episode (≥220 bpm lasting ≥5 minutes) is detected and stop taking it whenever these episodes have been absent for a predefined period. Criteria for initiation and interruption of anticoagulation are reasonably stratified according to the subject’s CHADS2 score. For instance, a 30-minute episode of arrhythmia prompts permanent anticoagulation in a subject with a CHADS2 score of 5 or 6, whereas a subject with a CHADS2 score of 1 or 2 is anticoagulated only if the arrhythmia has a duration of 48 hours and is instructed to discontinue anticoagulation after 30 consecutive days without detected arrhythmia.

Finally, intensive research is being conducted to refine our understanding of the mechanisms of thrombogenesis in AF. Although we usually think that AF leads to clot formation in the left atrium because of blood stasis caused by the abnormal atrial contraction, the pathophysiology underlying the thrombogenicity from AF is actually much more complex. It includes endocardial damage and dysfunction, activation of the inflammatory cascade, increased release of growth factors, and abnormal hemostasis (including platelet activation), to mention just a few additional mechanisms. The lack of temporal correlation between atrial tachyarrhythmias and embolic events in the TRENDS study (only 27% of patients had atrial tachycardia/AF within the 30 days preceding the embolic event, and only 15% had the arrhythmia at the time of the embolic event) is another piece of evidence defying a simplistic explanation for the thrombogenicity of AF. In fact, these data question the safety of discontinuing anticoagulation in patients with documented paroxysmal atrial tachyarrhythmias after a certain arrhythmia-free period, as contemplated in the design of IMPACT.

Prolonged ambulatory cardiac rhythm monitoring discloses the true prevalence of PAF and has begun to uncover another dimension in the relationship between AF and stroke. However, we still need to learn how best to apply this new information in clinical practice. More research is indispensable to define whether this promising diagnostic modality can help reduce the societal burden of AF-related stroke.

Disclosures

Dr Rabinstein’s institution received funding from CardioNet for the conduct of an investigator-initiated project (study was completed and relationship with the company is no longer active).

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**Key Words:** ambulatory care || atrial fibrillation || diagnosis || ischemic attack, transient || monitoring, ambulatory || stroke
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