

Cryptogenic Stroke and Role of Loop Recorder

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Abstract

Ischemic stroke is an important cause of morbidity and mortality when untreated. Identifying atrial fibrillation is important because atrial fibrillation ischemic related strokes are associated with an increased risk of disability and death compared with strokes of other etiologies and tend to recur without anticoagulation. However, atrial fibrillation detection can be difficult when it is asymptomatic and paroxysmic and may be the underlying cause of some cryptogenic strokes or strokes of unknown origin. In this review, the different methods of cardiac monitoring to detect atrial fibrillation in patients with cryptogenic stroke are summarized, with a focus on loop recorder monitoring.

Introduction

Ischemic Stroke is a disabling disease and leads to significant morbidity and mortality. Clinical and subclinical atrial fibrillation (AF) increases the risk of a stroke four fold and, indeed, is the predominant risk factor for cardioembolic stroke: in approximately 50% of cardioembolic strokes, AF is the source of cardiac emboli.^{1,2,3}

The self-terminating and often asymptomatic nature of paroxysmal atrial fibrillation (PAF) may lead to its underdetection and untreatment. Cryptogenic stroke has been defined as a cerebrovascular event of unknown origin, despite through work-up and represents 20- 30% of all ischemic strokes. Furthermore, reported rates of cryptogenic stroke recurrence vary across cohorts but may be high.⁴ The presence of occult PAF and uncovered atrial tachyarrhythmias (otherwise probably non-detected) by prolonged cardiac rhythm monitoring has been shown to be associated with increased risk of stroke in several studies of patients with implantable pacemakers and defibrillators.^{5,6} Therefore, it is likely that a proportion of strokes labeled as cryptogenic are cardioembolic in origin because of occult AF.^{7,8}

Detection of AF usually prompts long term anticoagulation instead of antiplatelet therapy because anticoagulation in AF related stroke has been proved to reduce morbidity by reducing the probability of recurrent stroke by two-thirds. Although two randomized trials are currently ongoing,^{9,10} at this point in time anticoagulation has no proven benefit in cryptogenic stroke when AF is not documented¹¹⁻¹⁴ and antiplatelet agents are recommended.¹⁵ Therefore, it is very

important to monitor cardiac rhythm in the presence of a cryptogenic stroke to detect AF and identify which patients will benefit from anticoagulation. The European Stroke Organization¹⁶ and the American Heart Association (AHA)/ American Stroke Association¹⁷ recommend that 24-hour-Holter monitoring is used to detect paroxysmic AF in patients with cardioembolic stroke as standard of care. More prolonged cardiac monitoring is recommended when AF is supposed.

The probability of detecting AF in cryptogenic stroke/TIA is highly variable depending on which strategy we use for monitoring and when it has been initiated after stroke/TIA episode.

There are several methods to detect AF in patients with cryptogenic stroke/TIA. In Table 1 these methods are summarized. They can be divided into noninvasive and invasive and they rely on skin surface electrograms and subcutaneous electrograms, respectively. The duration, diagnostic yield and price vary across the different methods. In general, the longer duration of the monitoring method, the higher the diagnostic yield and cost.¹⁸⁻²¹ AF can be detected also through intracardiac electrograms of dual-chamber pacemakers and implantable cardioverter defibrillators but these devices are not implanted for this purpose and are beyond the scope of this manuscript.^{5,6,22} In this review article, the electrocardiographic monitoring methods for detecting AF in cryptogenic stroke are summarized, with special emphasis on external and implantable loop recorders.²³

12-Lead Ecg , Holter And Ambulatory Telemetry

The detection rate of AF from a 12-lead ambulatory ECG after ischemic stroke or TIA is low, from 1% to 5%, as demonstrated by Bell C et al in a meta-analysis.²⁴ Shafqat S et al in a retrospective study of 210 consecutive patients with ischemic stroke that underwent 24-hour-Holter monitoring, AF was detected in only 5 cases (2,4%).²⁵ In a retrospective study, PAF lasting > 30 seconds was detected in only 2,4% in 413 patients with a definite ischemic stroke or TIA undergoing Holter monitoring for a mean of 22.6

Disclosures:
None.

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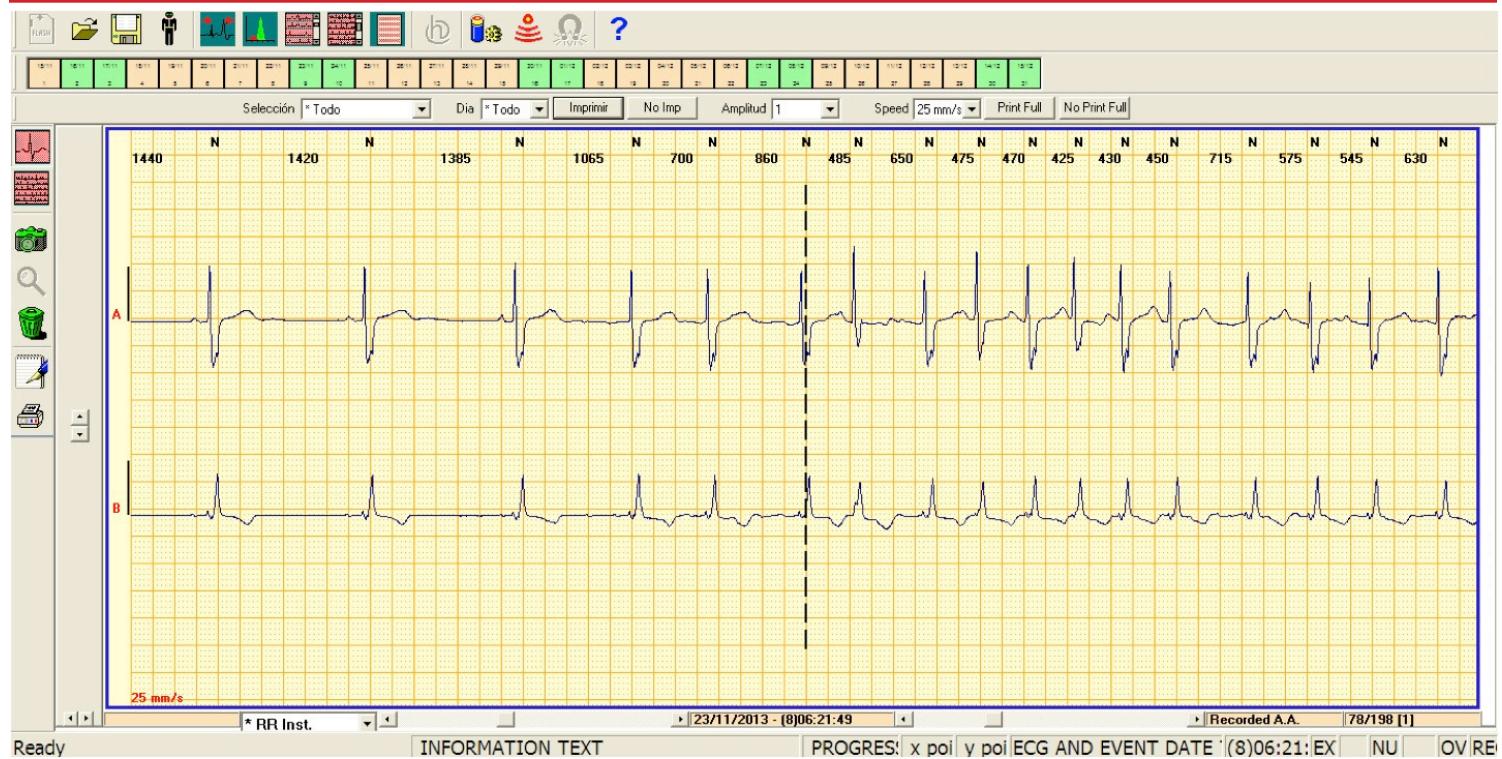


Figure 1: Automatic atrial fibrillation detected episode with the external loop recorder SpiderFlash-t TM, Sorin

hours.²⁶ Although ECG and 24-hour Holter monitoring are two not comparable techniques (a minimum time to diagnose AF, usually 30 seconds, is required in Holter monitoring and not in the ECG) the diagnostic yield of 24-hour Holter monitoring does not appear to be higher than the one of ECG. However, the diagnostic yield of Holter may be higher when monitoring is performed for more than 24 hours. Schuchert et al and Stahrenberg et al detected AF in 4.9% and 12.5% in their observational studies with a 72-hours-Holter and 7-days-Holter monitoring studies in patients with ischemic stroke or TIA, respectively. The interval from cerebrovascular event to monitoring strategy initiation were $\leq 14 - 21$ days in the former and 5,5h in the later. The definition of PAF were 60 seconds in the former and 30 seconds in the later.^{27,28} Furthermore, data provided by Holter may help to find patients more prone to have AF: in the study of Wallmann D et al, which included 127 patients with acute ischemic stroke, the presence of frequent premature atrial complexes ($\geq 70/24h$) in a 24-hour-Holter ECG was the only independent predictor of paroxysmal AF during follow-up (odds ratio 6.6, 95% confidence intervals 1.6 to 28.2, $P=0.01$).²⁹

Ambulatory cardiac telemetry can provide real time monitoring for up to 30 days. Data are transmitted by cellular network to a central monitor. Diagnostic yield of this monitoring strategy is highly variable (0% to 25%) because several PAF definitions have been used, some of them considering AF episodes less than 30 seconds. As in Holter monitoring, the AF detection rate is higher the greater the number of days of monitoring. Noncompliance reaches 36% probably due to the long period of monitoring.³⁰⁻³⁴

Loop Recorder Monitoring

General Characteristics

There are two types of devices: external loop recorders (ELR) and implantable loop recorders (ILR) which share some features. Basically, a loop recorder monitors the electrical activity of the heart

continuously. Once activated, data are stored for a programmable fixed amount of time before the activation (looping memory) and a period of time after the activation. Recording can be activated in two ways: automatically according to heart rate ranges previously defined and set, and through a hand-held patient activator pushed by the patient when they notice symptoms. Some of these devices, both external and internal, have algorithms specifically designed for the detection of AF, based not on a cutoff frequency, but on other criteria, such as the RR interval irregularity or P wave detection. The former devices are those recommended for detecting AF due to the possibility of detecting asymptomatic episodes and the ones not exceeding the programmed heart rate limits³⁵. Because PAF are so often asymptomatic, the patient-activated device function is much less useful in the context of a cryptogenic stroke. Data can be sent by the patient over the phone to a data center and physician notified based on pre-specified alerts or the patient may return the device to the outpatient for download. These devices are extremely sensitive and can uncover brief and asymptomatic episodes of PAF. Overreading of the pertinent tracings by a cardiologist is advisable.³⁶

External Loop Recorder Monitoring

ELR are small devices that are attached to the patient through chest electrodes or a wrist band and record the ECG for a maximum of 30 days. They are also referred to as event monitors or event recorders.³⁷ Because of the limited recording capacity of the ECG, the total AF burden can not be determined.³⁸ Despite a high sensitivity of 93% (comparable to ILR), specificity is lower, 51%, because of frequent artifacts.³⁰

There are several studies of external loop recorder monitoring with automatic AF detection algorithms in ischemic stroke or TIA (see Table 2). The majority have been observational, prospective or retrospective, evaluating a single type of device. Definitions of cryptogenic stroke/TIA were not uniform (different diagnostics

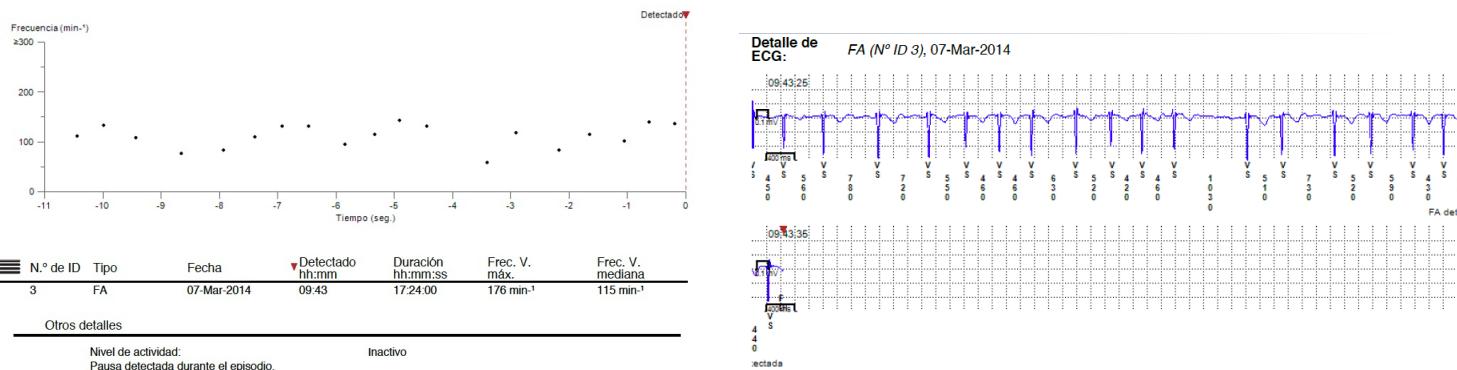


Figure 2 A and B: Automatic atrial fibrillation detected episode with the implantable loop recorder Reveal LINQTM, Medtronic

tests were used to reach the final diagnosis), one study included patients with remote AF, and intervals between cerebrovascular event occurrence and monitoring initiation were not homogenous. Because of this heterogeneity across the former studies and the lack of comparative trials among different devices, the rates of PAF detection are not strictly comparable. AF detection rate varies between 5.7% and 20% across the studies. The shorter the time required for PAF definition and the shorter the time interval between cerebrovascular event and monitoring initiation, the higher the diagnostic yield. This applies to the other types of ECG monitoring.^{38,40-45}

EMBRACE is the largest randomized trial on external loop recorder monitoring in patients with cryptogenic or TIA. It has proved superiority of external loop recorder over conventional strategy (24-hour-Holter monitoring) in detecting AF in patients with cryptogenic stroke or TIA occurred in the previous 6 months before randomization. Five hundred seventy-two patients 55 years or older were assigned to undergo ambulatory ECG monitoring with an event recorder (which incorporates an algorithm based on the irregularity of the RR interval that automatically detects AF) or with a 24-hour-Holter monitoring (control group). AF lasting 30 seconds or longer was detected in 45 of 280 patients (16.1%) in the event recorder, as compared with 9 of 277 (3.2%) in the control group (absolute difference, 12.9 percentage points; 95% confidence interval [CI], 8.0 to 17.6; $P < 0.001$; number needed to screen, 8). By 90 days, oral anticoagulant therapy had been prescribed for more patients in the intervention group than in the control group (52 of 280 patients [18.6%] vs. 31 of 279 [11.1%]; absolute difference, 7.5 percentage points; 95% CI, 1.6 to 13.3; $P = 0.01$).³⁸

Implantable Loop Recorder Monitoring

These leadless devices are inserted subcutaneously in the left

parasternal region with a very small incision. ECG signals are recorded through two electrodes within the device. Its longevity is 3 years approximately. Since 2010, the ILR have incorporated automatic AF detection capabilities. The sensitivity, specificity, positive predictive value, and negative predictive value for identifying patients with any AF with these devices are considerably high: 96.1%, 85.4%, 79.3%, and 97.4%, respectively. Furthermore AF burden (which may represent a useful measure of stroke risk) is accurately quantified when compared with an ECG Holter strip: Pearson coefficient = 0.97.⁴⁶

With the enhancement of the AF detection software, in which now the P wave detection is incorporated in the R-R interval pattern algorithm, the inappropriate episodes and duration are reduced by 46% and 55%, respectively, with a minimal reduction of appropriate episodes and duration by 2% and 0.1%, respectively. ILRs only detect AF episodes ≥ 2 minutes.⁴⁷

There are several studies that have attempted to analyze the ability of an ILR to detect AF in patients with ischemic stroke (see Table 2). Most of them are non-randomized, non-comparative studies. All of them have only included patients with cryptogenic stroke (not TIA, not patients with remote AF). All but one, have used an ILR with automatic AF detection capabilities. Despite a minimum AF detection time of 2 minutes, the diagnostic yield is higher (AF detection rate of 20-36%) than using a conventional Holter strategy and it may be also higher than using an ELR with automatic AF detection capabilities (although comparative studies between ILR and ELR are lacking). However, ILR offers a longer follow-up.⁴⁸⁻⁵³

CRYSTAL AF is the only randomized study that have compared ILR with a conventional monitoring strategy. Sanna T et al randomized, in a 1:1 ratio, 441 patients with cryptogenic stroke

Table 1:

Features of different methods for cardiac monitoring in patients with cerebral ischemia

Device	Invasiveness	Location	Duration	Minimal Threshold	Diagnostic Yield	Cost (\$)	Advantages	Disadvantages
12 lead ECG	Noninvasive	Skin surface	Seconds	Seconds	1-5 %	39 - 47 (Ref. 18)	-Low cost	-Low diagnostic yield
24 - 48 hour-Holter	Noninvasive	Skin Surface	Usually 24-48 hours	Seconds	2,4 %	178 (Ref. 19)	-Continuous recording	
Ambulatory Telemetry	Noninvasive	Skin Surface	≤ 30 days	Seconds	0 - 25 %	660 (Ref. 20)	-Continuos recording	
External loop recorder	Noninvasive	Skin Surface	≤ 30 days	Seconds	5.7-20 %	534 (Ref.19)	-Long duration -High diagnostic yield -Correlation of symptoms and rhythm	-Expensive -Patient participation -False positive
Implantable loop recorder	Minimal invasive	Subcutaneos	3 years	2 minutes	20 - 36 %	2925 (Ref. 21)	-Long follow-up -High diagnostic yield -Remote monitoring	-Expensive -Minimal invasive -Not possible to record short AF runs

Table 2:

Studies of loop recorder monitoring in patients with ischemic stroke or TIA

Study [ref]	No. of patients	Study design	Mean age (y)	Study population	Interval from CV event	Definition of PAF	Detection Method	Duration of monitoring	Diagnostic Yield
Barthélemy JC et al [9 bis 19]	60	Prospective cohort	64.0 ± 16.3	Any TIA or stroke (including 28 with CS or CTIA)	Mean 10 ± 2 d	30 s	aELR	4 d (70±31 h)	20% whole cohort, 14.3% CS/CTIA
Jabaudon et al [9 bis 20]	88	Prospective cohort	72 (56-91) in the AF group and 66 (37-93) in the non-AF group	Any TIA or stroke (patients with remote PAF were not excluded)	Mean 55 d	NA	aELR	7 d	5,5%
Elijovich et al [9 bis 21]	20	Retrospective cohort	68 ± 14	CS or CTIA	NA	30 s	aELR	≤ 30 d	20%
Flint et al [9 bis 22]	239	Prospective cohort	64.6 ± 13.8	CS	Mean 29 d (17 - 50)	5 s	aELR	≤ 30 d (24.5 ± 9 d)	12.1%
Higgins et al [9 bis 23]	100	Randomized trial	65.8 ± 12.3	Any TIA or stroke without known AF	≤ 7 d	Non-sustained: 6 VC Sustained: 20 s	aELR	7 d	Any: 44% Sustained: 18%
EMBRACE [9 bis 17]	572	Randomized trial	72.5 ± 8.5	>55 y CS or CTIA	Mean 75.1 ± 38.6 d	30 s	aELR	30 d	16.1%
Dion F et al [15]	24	Prospective cohort	49±13.6	<75 y CS	Mean 3 ±1.1 m	Any duration	ILR	14.5 m	4%
Mercé J et al (13)	14	Prospective cohort	65.4 ± 10.9	CS	< 1 m	2 min	aILR	29 ± 5.9 m	36%
Cotter PE et al [16]	51	Prospective cohort	Median 52 (17 - 73)	CS	NA	2 min	aILR	116 d	25.5%
Etgen T et al (17)	22	Prospective cohort	65.8 (45.3-86.4) in the AF group and 60.0 (54.4-65.6) in the non AF group	CS	NA	≥ 6 min	aLR	12 m	27.3 %
SURPRISE study (18)	85	Prospective cohort	66.9 in the AF and 54.0 in the non -AF group	CS	Mean 107 ± 117 d	2 min	aILR	Mean 569 ± 310 d	20.7%
CRYSTAL AF (12)	441	Randomized trial	61.5 ± 11.3	> 40 y CS	Mean 48 d approx.	2 min	aILR	36 m	30%

aELR= automatic AF detection external loop recorder; aILR = automatic AF detection implantable loop recorder; AF = atrial fibrillation; CS = Cryptogenic stroke; CTIA = Cryptogenic transient ischemic attack; d = day/s; h = hour/s; ILR = implantable loop recorder without ; min = minute/s; m = month/s; NA = not available; PAF = paroxysmal atrial fibrillation; s = second/s; TIA = Transient ischemic attack; VC = ventricular complexes

to receive an ILR or to a conventional follow-up which comprised ECG monitoring at the discretion of the site investigator. ILRs were connected to Medtronic CareLink Network to remotely transmit the device data. Maximum follow-up was 36 months and follow-up visits were scheduled at 1,6 and 12 months and every 6 months thereafter. By 6 months, AF had been detected in 8.9% of patients in the ILR group (19 patients) versus 1.4% of patients in the control group (3 patients) (hazard ratio, 6.4; 95% confidence interval [CI], 1.9 to 21.7; $P<0.001$). By 12 months, AF had been detected in 12.4% of patients in the ILR group (29 patients) versus 2.0% of patients in the control group (4 patients) (hazard ratio, 7.3; 95% CI, 2.6 to 20.8; $P<0.001$). At 36 months of follow-up, the rate of detection of AF was 30.0% in the ILR group (42 patients) versus 3.0% in the control group (5 patients) (hazard ratio, 8.8; 95% CI, 3.5 to 22.2; $P<0.001$). Although the superiority of the ILR for detecting AF resulted in a higher rate of use anticoagulation (14.7% versus 6.0% at 12 months in the ILR and control group respectively $P = 0.007$), the recurrent ischemic stroke or TIA incidence was not statistically different between groups (7.1% versus 9.1% in the ILR and control group respectively at 12 months follow-up). Seventy-nine percent of AF episodes detected in this study at 12 months follow-up were asymptomatic.⁴⁸ This finding, in combination with the paroxysmal nature of atrial fibrillation after cryptogenic stroke, may account for the low yield of diagnostic strategies based on symptom occurrence or the use of intermittent short-term recordings.

These devices (ELR and ILR) have some limitations. First, they have false positives caused by noise, intermittent T wave oversensing,

frequent premature ventricular or supraventricular complexes, sinus arrhythmias or sinoatrial blocks.^{46,49,54} Second, they have a limited memory and once the storage capacity is met, data on the oldest episodes are discarded in order to record new episodes. So, theoretically a true positive AF episode may be erased by a false positive AF episode occurred later. Third, they are expensive. Therefore, it seems reasonable to indicate them to those patients most likely to have occult PAF and when anticoagulation is needed if PAF is encountered. The main risk factors for AF detection are: older age, coronary artery disease, high CHADS2 or CHA2DS2-VASc score, sever stroke, frequent premature atrial complexes, left atrial dilatation, left atrial appendage dysfunction and a particular embolic pattern on brain imaging (multiterritorial or single cortical-subcortical infarctions).^{29,40,55}

In figures 1 and 2 an automatic AF detection episode is shown with an ELR and ILR respectively.

Gaps And Lines Of Future Research

The superiority of the loop recorder to Holter monitoring is evident. However, it is unclear if newly discovered AF is always the etiology of the index stroke, particularly when the detected AF episodes are brief. There are some unsolved issues in this field.

Despite methods of prolonged cardiac monitoring are expensive, they may be cost-effective. According to the study of Kamel H et al, one week of cardiac monitoring (ECG, Holter, Telemetry or Loop recorder) after ischemic stroke to detect AF would be cost-effective.⁵⁶ Research on cost-effectiveness of more prolonged

monitoring in the setting of an ischemic stroke of unknown origin is lacking and warranted.

There have been described some surrogates markers for AF detection in cryptogenic stroke. Fonseca AC et al. showed in their prospective study that a N-terminal probrain natriuretic peptide > 265.5 pg/ml was a biomarker of cardioembolic stroke (in comparison to noncardioembolic stroke) with a sensitivity and specificity of 71.4% and 73.7% respectively.⁵⁷ A decreased left atria strain (deformation) is also an independent marker for detection of AF in cryptogenic stroke.⁵⁸ Further studies are needed to determine which risk factors identify the patients who would derive the most clinical benefit from detection of AF by prolonged monitoring with an ELR or ILR.

Does the well established benefit of anticoagulation in patients with ischemic stroke or TIA and detected AF by conventional methods (ECG, bedside telemetry, 24–48 hour Holter monitoring) apply also when AF is detected by prolonged monitoring strategies (which may imply less PAF burden)? Does the magnitude of the benefit of anticoagulation depends on the AF burden? In other words: are the results of prolonged monitoring useful to guide anticoagulation? Further research in these issues is required.

What are the optimal timing and duration of cardiac monitoring? In which setting (outpatient or in patient)? What is the optimal monitoring device? Further studies are needed to answer these questions.

Conclusions:

Loop recording monitoring is superior to a conventional monitoring strategy and may be considered after a cryptogenic stroke or TIA in patients who are good candidates for anticoagulation. However, the optimal use of these diagnostic techniques and the therapeutic implications of the findings remain to be established.

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