Curr Treat Options Neurol (2016) 18: 17
DOI 10.1007/s11940-016-0400-y

Cerebrovascular Disorders (HP Adams, Section Editor)

The Evolution and Application of Cardiac Monitoring for Occult Atrial Fibrillation in Cryptogenic Stroke and TIA

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Published online: 29 February 2016
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This article is part of the Topical Collection on *Cerebrovascular Disorders*

Keywords Cryptogenic stroke · Cardiac monitoring · Atrial fibrillation · Holter · Telemetry · Loop recorder

Opinion statement

The evaluation of the stroke and transient ischemic attack (TIA) patient has been historically predominated by the initial evaluation in the hospital setting. As the etiology of stroke has eluded us in approximately one third of all acute events, the medical community has been eager to seek the answer to this mystery. In recent years, we have seen an explosion of innovations and trends allowing for a more detailed post stroke assessment strategy aimed at the identification of occult atrial fibrillation as the etiologic cause for the cryptogenic event. This has been achieved through the evolution and aggressive application and study of prolonged and advanced cardiac monitoring. This review is aimed to clarify and elucidate the standard and novel cardiac monitoring methods that have become available for use by the medical community and expected in the higher level care of cryptogenic stroke and TIA patients. These cardiac monitoring methods and devices are as heterogeneous as our patient population and have their own advantages and disadvantages. Many factors may be taken into consideration in choosing the appropriate cardiac monitoring method and are highlighted for consideration in this review. With a judicious approach to investigating the cryptogenic stroke population, and applying a wealth of novel treatment options, we may move forward into a new era of stroke prevention.

Introduction

Cryptogenic stroke and its association with occult atrial fibrillation (AF) have experienced a wealth of attention in recent years. Much of this revival of interest in detecting AF stems from advancements in cardiac monitoring in the post-stroke period. These advancements have shown increasing levels of occult AF detection and have been paired with various innovations in both medical and procedural approaches to AF-related stroke risk reduction. Currently, there are numerous types and brands of monitoring devices available with improvements on existing designs and new products introduced annually. While we will not discuss specific brands in detail, it is important to consider the capabilities and limitations of each device and different monitoring methods to ensure that the appropriate medium is selected in the search for AF detection.

As it stands, regulatory standards for post-stroke cardiac monitoring have only recently appeared in guidelines. While recommendations have supported prolonged monitoring, they have remained nonspecific [1••, 2••], and our experience is that insurance companies have been inconsistent in their approval of certain methods of monitoring. In 2014, shortly after the low level evidence recommendations were published, two randomized controlled trials (RCTs) demonstrated benefit of prolonged monitoring, thereby providing level 1 evidence for this approach [3•, 4•]. Despite this, there are still many variables to consider and the growing number of options available will only increase the complexity of decision making, emphasizing the need for clearer regulatory guidance.

Electrocardiography and inpatient telemetry

Current recommendations call for a 12 lead electrocardiography (ECG) at baseline and at least 24 h of ECG monitoring for patients with acute stroke or TIA [5]. These recommendations represent a bare minimum for cardiac monitoring in the acute stroke setting and do offer some diagnostic utility. A meta-analysis on cardiac monitoring after stroke reported that admission ECG detected 7.7 % of AF in patients without a known history of AF in 11 studies [6]. This report also summarized nine studies reporting a 5.6 % detection rate with the use of serial ECGs while inpatient, and five studies reporting a 7 % detection rate with continuous ECG monitoring while inpatient. There was also a 4.1 % detection rate for inpatient telemetry in 6 studies and 4.5 % detection rate with the use of inpatient Holter monitoring in 16 studies [6].

These results highlight the first opportunities for detecting and subsequently diagnosing occult AF and may offer some additional insight into the risk of future development or discovery of paroxysmal AF even if AF is not captured during this initial monitoring phase. Considering the various capabilities of acute inpatient monitoring in facilities across the world, it is important to consider that any one of these strategies may be of significant value if applied judiciously. A center with limited resources may not have inpatient telemetry and, however, may arrange for a Holter monitoring service or at least serial ECGs to ensure that the prospect of capturing occult AF is not missed. The 12 lead ECG could be considered the most accurate method of confirming AF but is not feasible to be run continuously in most cases; therefore, the use of one or two-channel telemetry to detect potential AF episodes in real time provides a sufficient cause for repeating a 12 lead ECG to reliably confirm the arrhythmia. Holter monitoring does not currently allow for real-time triggering of a potential arrhythmia but has some potential for gathering other information like premature atrial complexes (PACs) and deviations in heart

rate. In the acute monitored setting, pieces of gathered information—PACs, demographic, and echocardiographic features—are sometimes overlooked but can aid in stratifying patients into low- or high-risk candidates for detection of paroxysmal AF with subsequent cardiac monitoring. All centers caring for acute stroke patients should have an internally delineated protocol for the screening and/or monitoring of cardiac arrhythmias in the in-hospital phase of their evaluation.

Holter monitoring

The "Holter" monitor (HM) was first described by Norman J. Holter in 1961 and included a backpack ECG device weighing 75 lbs [7]. Prior to the plethora of recently developed extended duration monitors, HMs had been the first-line monitoring device for patients at risk of AF after stroke of suspected cardioembolic etiology. Regarding AF detection reported with the use of the Holter monitoring strategy in the ambulatory setting, there was an average AF detection rate of 10.7 % in 13 studies [6]. However, significant variability in the results was also seen, with as low as 1.7 % over 7 days in one study [8] and as high as 42 % in another where it also showed a higher AF detection rate than ECG (11 vs 42 %) [9]. In two randomized controlled trials, 24-h Holter monitoring was used as the "bare minimum" monitoring standard for comparison against the more prolonged monitoring strategies and was shown to have significantly lower yield than those strategies (3.2 vs 16.1 % at 90 days and 1.4 vs 8.9 % at 6 months) [3•, 4•]. Other studies have utilized the presence of PACs and atrial runs recorded on Holter monitoring as quantifying features to determine the associated risk of AF detection with more prolonged monitoring methods, and in some cases, directly with risk of stroke [10–15].

Due to a finite storage capacity, an HM evaluation is typically limited to 24–48 h, although several newer renditions are capable of up to 7–14 days of monitoring. There are numerous types and brands of HMs, each with their own specifications, lead arrangements, and accuracy of arrhythmia detection. Traditionally, HMs have multiple leads and produce multichannel tracings, a design that maximizes quality at the expense of reduced convenience. Some of the newest versions of Holter-like monitors are utilizing a compact or "patch" design that can provide single channel data for up to 14 days without the need for wire based leads, thereby maximizing convenience and relative monitoring duration (Fig. 1). This convenience comes with an unclear effect on tracing quality as the placement of leads become invariably closer together; however, one study suggested very good reliability of the patch device when simultaneously compared to a 3-channel Holter [16]. Holter devices generally are capable to completely store the information captured and permit review and analysis at a later time. This usually occurs after being returned to the office or mailed back to the service provider, although directly uploading the data from one's home computer or interfacing with one's smartphone are other innovative options that are likely to be available on some of the newer and compact models. Holter Monitors, depending on device specifications, may provide single channel or multichannel data and are also typically able to quantify the number of PACs or supraventricular ectopic beats, which may be utilized in risk stratification for further monitoring. Additionally, they are more accessible and cost-effective. The main drawbacks of HMs remain the limited duration of monitoring and lack of real-time reporting of results.

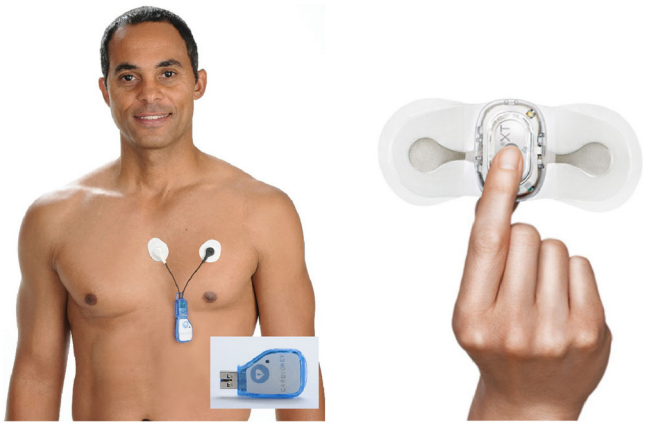

Fig. 1. Compact cardiac monitoring devices. "Compact" 14-day holter monitor (*left*) and 14-day "Patch" monitor (*right*). Images courtesy of Biotelemetry Inc. and iRhythm Technologies Inc., respectively.

External loop recorders and mobile cardiac telemetry

External loop recorders (ELR) or event monitors (EM) were the next devices to arrive on the scene and afforded the ability to capture discrete or rare events that might not be detected during the brief time period an HM could be worn. These surface monitors began predominantly as symptom triggered devices dependent on the patient to identify an abnormal symptom such as a palpitation or syncopal spell. They have since evolved and now frequently utilize AF detection algorithms in order to automatically detect asymptomatic arrhythmias, an essential feature for our purpose of AF detection as most AF episodes are asymptomatic [17]. Typically, like HMs, these devices must be analyzed after return of the device but may be less expensive than other services like outpatient telemetry or implantable monitors. ELRs generally have limited memory capacity and may overwrite older tracings if too many events occur prior to uploading of the data. The most notable study employing an ELR was the randomized controlled trial EMBRACE, which showed a 16.1 % AF detection rate against 24-h Holter monitoring [3•]. A meta-analysis of ELR studies reported a similar overall rate of 16.2 % AF detection [6].

Mobile cardiac outpatient telemetry (MCOT) was first studied for occult AF detection in cryptogenic stroke by Tayal et al. in 2008 where they reported a 23.2 % overall AF detection rate with 21 days of monitoring [18]. MCOT differs from ELR in that it transmits two-channel ECG tracings wirelessly to the monitoring center for additional verification, review, and real-time reporting to the ordering physician (Fig. 2). This allows the physician to act on the findings promptly, prior to completion of the monitoring period. One of the most commonly utilized MCOT devices in the USA has reported 100 % sensitivity and positive predictive value, as compared to a standard Massachusetts Institute of Technology-Beth Israel Hospital (MIT-BIH) arrhythmia database. This device employs an AF detection algorithm, including P-wave sensing and QRS morphology analysis, along with the more standard rate and R-R interval variability analysis. In the meta-analysis by Sposato et al., an overall 15.3 % detection rate was reported for MCOT with the largest study of 156 patients reporting a 17.3 %

Fig. 2. Outpatient cardiac telemetry. Mobile cardiac outpatient telemetry, courtesy of Biotelemetry Inc.

detection rate [6, 19]. Similar to most of the other external monitoring devices, MCOT is able to detect brief episodes of 30 s or longer reliably but may also report episodes lasting <30 s, a finding that has been frequently reported in these studies [18–20]. The detection of AF <30 s has led to considerable debate regarding the significance and preferred treatment for such episodes [21].

ELRs and MCOT offer similar durations of monitoring and have been studied with good detection of occult AF within a relatively short duration of monitoring (<30 days). Like most devices within a single category of monitoring, there is the potential for significant differences between two monitoring strategies, which is also true for ELR and MCOT. ELRs do not usually offer real-time reporting, which may result in a delay in diagnosis; however, it is offered at an overall cost savings and may be approved by some insurance companies, where MCOT is not. MCOT, on the other hand, arguably has a more rigorous evaluation and reporting process, along with having one of the few randomized comparative studies showing a reported advantage over ELR for clinically significant arrhythmia detection (41 vs 15 %, $p < 0.001$) [22]. At the time of this study, many ELRs did not have automated AF detection algorithms, and although there was still better detection with MCOT than those ELRs that had AF detection algorithms, it is possible that the AF algorithms have become more advanced since that time.

Implantable loop recorders

Implantable loop recorders (ILRs) represent the newest iteration of devices utilized to detect occult aberrant heart rhythms, including AF (Fig. 3). In contrast to external cardiac monitors (ECMs), such as HMs, ELRs, and MCOT, ILRs are arguably less hampered by patient compliance and can monitor for considerably longer periods of time [23, 24]. The randomized trial CRYSTAL AF [4•] reported a 6-month detection rate of 8.9 % and a 1-year detection rate of

Fig. 3. Implantable loop recorder. Insertable cardiac monitor and upload monitor. Reproduced with permission of Medtronic, Inc.

12.4 % of AF in patients with cryptogenic stroke or TIA, which improved to 30 % after 3 years of protracted monitoring. Notably, the device in this study does not detect AF episodes less than 2 min in duration due to its method of AF detection [4•]. Another study randomized post-AF ablation patients to either a Permanent Pacemaker (PPM) Holter or an ILR for detection of AF events. They found that 26 % of ECGs were uninterpretable in the ILR group, and the sensitivity and specificity were reduced for ILR as compared to PPM Holter (79 vs 100 % and 66 vs 98 %, respectively, $p < 0.001$), while another study found similar sensitivity issues with the ILR [25, 26]. In addition to the reported sensitivity and specificity issue, ILRs also carry a substantially higher cost than ECMs; however, the significantly prolonged duration of monitoring afforded by ILRs (up to 36 months) allows for a potentially higher likelihood of capturing rare events and arrhythmias over time. In a meta-analysis of ILR studies, these devices detected AF by the primary endpoint at an overall rate of 16.9 % in seven studies, although it has been reported to detect as high as 33.3 % at 1 year in a study that applied a risk stratification process [6, 10].

Regarding price, it is estimated that an ILR device costs about $4000–$5000 (€3640–€4554) with additional charges for implantation, explantation, and monitoring thereby raising the total price to about $7400 (€6740). Plans for a study to confirm the safety of in-office implantation instead of the current process of in-hospital implantation in a surgical suite may reduce the total cost by an estimated $727–$857 (€662–€781) if in-office implantation is approved [27–29]. While ILRs occasionally need to be prematurely removed due to skin reaction, infection, or discomfort reasons, they carry a low risk of significant complications and implantation remains a minimally invasive procedure [23, 26, 30].

ILRs have been employed in patients with unexplained recurrent syncope with such a high level of success that the European Heart Rhythm Association (EHRA) has given Class I recommendations for its use in patients with recurrent syncope of undetermined etiology [23, 30–32]. These patients are choice candidates for extended monitoring as their symptoms occur sporadically and without warning, which may be analogous to patients with rare paroxysmal and/or asymptomatic AF, assuming an arrhythmia duration of greater than 2 min. Given the large morbidity and mortality that result from patients who suffer a stroke, especially from a cryptogenic etiology, determining the cause and ultimately preventing recurrent strokes are of the highest priority for most neurologists. The capability of a long-term monitoring option is quite valuable to detect these occult and asymptomatic AF episodes, in particular if other

methods of cardiac monitoring have failed to detect AF [4•, 31, 33]. To balance its limitations, it would be desirable for future derivations of ILRs to be more cost effective, to have more reliable AF detection capabilities per unit time, and to have more regulatory guidance directing its use due to its invasive nature and higher cost.

Risk stratification

With recent heightened focus on monitoring of patients with cryptogenic stroke or TIA, along with guidelines beginning to recommend routine monitoring, the potential for a significant expenditure of medical dollars toward cardiac monitoring is a real concern. It is prudent for physicians to consider the pretest probability of cardiac monitoring detecting AF and consider the depths to which they plan to investigate that possibility. Over the years, the cardiology and stroke communities have uncovered a wealth of data regarding predictive risk factors for detection of AF, and we may be able to apply this information to stratify our use of resources more wisely, especially when cost is a concern. A recent study using a risk stratification scheme was able to show a nearly 3-fold increased yield of detection over a comparable study with the same device (33.3 vs 12.4 % at 12 months) [4•, 10].

Several factors are known to increase the risk of AF development, and many of these have been noted in the cryptogenic stroke population (Table 1). Increasing age, female gender, hypertension, diabetes, obesity, obstructive sleep apnea, mitral valve dysfunction, left atrial dilatation, PACs, reduced left ventricular ejection fraction, prior or current infarcts on imaging, and higher NIHSS severity are some of the significant associations that have been detected in various studies [10, 12, 13, 15, 18, 19, 34–40]. Infarct topography or pattern in acute stroke was previously reported as suggestive of etiology in a 2003 study; although this finding has been somewhat inconsistent, the finding of multiplicity of acute infarcts in one recent study showed a strong correlation (OR 11.1, 95 % CI 2.5–48.5, $p < .01$), and other studies reported that the increasing presence of acute or chronic infarcts also increased the risk of AF [19, 34, 38, 41]. PACs are also important and of considerable value when discussing cardiac monitoring. Several studies have shown that excess PACs or supraventricular ectopic beats detected on Holter correlated with AF detection on ensuing monitoring [12, 13, 15, 42]. An additional article found that the chance occurrence of a PAC on baseline ECG correlated with a 61.9 % rate of detection (HR 13.7 (2.7–68.6), $p = 0.001$) on subsequent MCOT monitoring [19]. PAC quantification via 24-h Holter monitoring was used to identify high-risk candidates for the 2015 study of Poli et al., again, underlining its importance in the detection of AF [10]. Utilizing the aforementioned clinical, echocardiographic, and demographic risks, along with findings on initial electrocardiographic evaluation, patients could be stratified by level of risk and further diagnostic modalities could be tailored to the individual patient. A study in 2009 by Suissa et al. proposed a Score for the Targeting of Atrial Fibrillation (STAF) using the risk associations collected from 456 consecutive patients with ischemic stroke; however, the value of this score has been questioned in one study with a sensitivity and specificity reported at 79 and 74 %, respectively, for predicting AF [37, 43].

Table 1. Atrial fibrillation predictive risk factors

Study	Monitoring method	Risk factors	Odds ratio or hazard ratio (95 % CI) for AF detection
Bernstein et al. [34]	ICM for 12 months	Chronic infarct on brain imaging:	
		Any chronic lesion(s)	HR 2.84 (1.13–7.15), $p = 0.02$
		Territorial	HR 2.37 (0.98–5.72), $p = 0.05$
		Leukoaraiosis	HR 2.94 (1.28–6.71), $p < 0.01$
Wallmann et al. [12]	Event-record monitoring for 7 days at 0, 3, and 6 months	Presence of frequent PAC	OR 6.6 (1.6–28.2), $p = 0.01$
Miller et al. [19]	MCOT for 21 days	Female gender	HR 6.2 (1.9–19.5), $p = 0.002$
		Presence of PACs	HR 13.7 (2.7–68.6), $p = 0.001$
		Left atrial diameter (increase by 1 cm)	HR 2.3 (1.1–5.0), $p = 0.033$
		Left ventricular ejection fraction (decrease by 10 cm)	HR 1.8 (1.2–2.7), $p = 0.008$
		NIHSS (increase by 1 point; for stroke patients only)	HR 1.2 (1.1–1.4), $p = 0.008$
Poli et al. [10]	ICM for 12 months	Presence of atrial runs	HR 2.7 (1.2–6.7), $p = 0.023$
		Left atrial size > 45 mm	HR 3.6 (1.6–8.4), $p = 0.002$
Thijs et al. [35]	ICM for 12 months	Age (every decade increase)	HR 1.91 (1.31–2.80), $p = 0.0009$
		PR interval (every 10 ms increase)	
		- On PR interval prolonging medication	HR 1.17 (1.02–1.35), $p = 0.02$
		- Off PR interval prolonging medication	HR 1.58 (1.32–1.90), $p < 0.0001$
Kamel et al. [36]	Pooled analysis from four clinical trials	Age (every decade increase)	HR 1.6 (1.4–1.9), $p < 0.005$
		Female gender	HR 1.7 (1.2–2.4), $p < 0.005$
		Congestive heart failure	HR 1.9 (1.1–3.4), $p = 0.02$
		Absence of hypertension	HR 1.6 (1.1–2.2), $p = 0.01$
Tayal et al. [18]	MCOT for up to 21 days	Diabetes mellitus	OR 6.15 (1.16–32.73), $p = 0.033$
Suissa et al. [37]	ECG or Holter monitoring for 24 h	Age > 62 years	OR 11.8 (5.3–26.0)
		NIHSS ≥ 8	OR 3.8 (2.0–7.4)
		Left atrial dilation	OR 12.3 (5.2–28.9)
		Absence of vascular etiology of stroke	OR 36.2 (15.8–82.6)
Alhadramy et al. [38]	Holter monitoring for mean 22.6 h	Age (every year increase)	OR 1.1 (1.0–1.1), $p < 0.0001$
		Number of acute infarcts on MRI	OR 11.1 (1.4–86.4), $p = 0.0220$
		Number of chronic infarcts on MRI	OR 3.0 (1.7–5.1), $p < 0.0001$
		Acute cortical infarcts on CT/MRI	OR 5.8 (1.9–17.8), $p = 0.0023$

Table 1. (Continued)

Study	Monitoring method	Risk factors	Odds ratio or hazard ratio (95 % CI) for AF detection
Gladstone et al. [15]	ELR for 30 days	Number of premature atrial beats per 24 n:	AFib detection rate:
		<100	7–9 %
		100–499	9–24 %
		500–999	25–37 %
		1000–1499	37–40 %
		>1500	~40 %
Skaarup et al. [39]	Echocardiography findings	Risk factor	AF vs non-AF
		Left atrial minimal volume (mL)	30 ± 17 vs 24 ± 10, $p = 0.035$
		Left atrial emptying fraction (%)	45 ± 10 vs 50 ± 10, $p = 0.004$

Adjusted OR and HR are mentioned whenever available
OR odds ratio, *HR* hazard ratio
p values are mentioned whenever available

Choosing a cardiac monitor device

Without a doubt, choosing the ideal monitoring strategy can become a complex endeavor if attempting to compare the pros and cons of every monitoring device at each phase of evaluation, although many reasonable options and approaches exist. The process should begin with the evaluation of the patient, including demographics, stroke characteristics and echocardiographic findings, and then determining the associated pretest probability of AF presence. All patients should be evaluated with a 12 lead ECG and at least 24 h of in-patient telemetry or HM, depending on the availability at each center. Further evaluation for those with reasonable ongoing suspicion for occult AF should prompt the decision for 7–14 days of HM, 21–30 days of ELR or MCOT, or commitment to long-term implantable monitoring. Any of these choices are reasonable as the next step in evaluation, but several factors should be considered when making this choice. If an evaluation with an HM, ELR, or MCOT is negative, you should be prepared to decide, along with the patient, if the pretest probability of continued monitoring with an ILR is likely to produce a treatable diagnosis.

A patient with minimal predictive risk factors and a negative initial evaluation may not require long-term monitoring with an ILR, and the additional expenditure of health care dollars can be avoided without a significant risk of missing occult AF. Alternatively, a patient with considerable pretest risk and low probability of compliance with an external monitor might be a reasonable candidate for ILR as the initial choice. These authors recommend a graded escalation of monitoring with a fluid consideration of ongoing risk of AF detection at each stage of monitoring for most cryptogenic stroke/TIA patients. We also recommend considering the cost of each type of monitoring along with the characteristics and specifications of any monitoring device—including the AF detection sensitivity and specificity of

the proposed device—and sharing these considerations with your patient. At this time, there are minimal quality studies directly comparing the various prolonged monitoring devices or strategies.

Atrial fibrillation and options for treatment

Over the past few years, the evolution of cardiac monitoring has coincided with the vast expansion of AF treatment options. Long overdue was an alternative to vitamin K antagonists (VKA) with the emergence of the novel oral anticoagulants (NOACs). The RE-LY trial marked the first RCT to confirm an alternative to VKA with its direct thrombin inhibitor and has since been followed by several factor Xa inhibitors, each of which come with their own specific considerations [44–47]. Some advantages include the lack of required laboratory monitoring as well as a reduction in intracranial bleeding over VKAs; however, the prerequisite of adequate renal function and a significantly higher cost are two notable disadvantages [44–47]. Reversibility of the anticoagulant effects of the NOACs has been the subject of consternation for many, although recent publications showing effective reversal agents will likely stem this concern [48, 49]. Another area of debate has surfaced surrounding the increasing number of very short paroxysms of AF detected by the increased amount of cardiac monitoring and has been estimated to account for more than half of cases detected after stroke or TIA [20]. While clearly, more study is needed to determine the significance and most appropriate treatment strategy for these short paroxysms of AF, it appears that neurologists are more likely to anticoagulate cryptogenic stroke or transient ischemic attack patients with AF episodes <30 s than are cardiologists [21].

For the most part, NOACs have provided another option only to those patients deemed appropriate for anticoagulant therapy, but not necessarily to those many patients deemed unable to receive anticoagulant therapy. The only exception was seen in the AVERROES study, which compared the factor Xa inhibitor to aspirin alone in patients not suitable for VKA therapy. It revealed that this NOAC was significantly more effective at preventing stroke and there was no increase in major bleeding or intracranial hemorrhage, and overall, remained safer than aspirin therapy [50]. An alternative to anticoagulation exists in the left atrial appendage occlusion device, WATCHMAN, for patients deemed unsuitable or unwilling to take long-term anticoagulants. Based on the findings of the ASAP, PROTECT AF, and PREVAIL trials, it has also received the CE mark of approval for marketing in Europe and approval by the FDA in the USA [51–53]. Another alternative is the LARIAT, which is a 510-k FDA cleared pericardial and trans-septal left atrial appendage suturing device aimed at isolating the left atrial appendage and reducing the risk of cardioembolism [54]. Each of these strategies come with restrictions, caveats, advantages, and disadvantages, as well as the potential for the unknown complication. It is therefore crucial to make an informed and patient-tailored decision.

Conclusion

Occult paroxysmal atrial fibrillation detection and treatment have become one of the most important areas of evaluation in the post-acute stroke period. The multitude of treatment and diagnostic options available, in conjunction with

the rapid evolution of cardiac monitoring devices, has allowed for the resurgence of interest into the investigation of the cryptogenic stroke patient. The variability and complexities of these monitoring strategies have created uncertainty in determining the best approach. While longer monitoring with any single device intuitively increases detection of AF, we must also remember that each device is unique with advantages and disadvantages, and the ultimate choice should be customized to the individual patient's needs. It is clear that cardiac monitoring will remain an important part of the cryptogenic stroke patient evaluation. How risk factors are used to stratify monitoring strategies and how resources are utilized in the presence of mounting health care costs remain uncertain and warrants continued investigation.

Acknowledgments

A special thank you to Dr. Myrna Rosenfeld for taking the time to review this manuscript.

Compliance with Ethical Standards

Conflict of Interest
Daniel J. Miller, Kavit Shah, Sumul Modi, Abhimanyu Mahajan, Salman Zahoor, and Muhammad Affan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Culebras A, Messé SR, Chaturvedi S, Kase CS, Gronseth G. Summary of evidence-based guideline update: prevention of stroke in nonvalvular atrial fibrillation Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014;82(8):716–24.

This guideline provides the most up to date evidence based approach to patient management in the prevention of stroke in non-valvular atrial fibrillation. However, additional evidence has surfaced as referenced in this review that has not yet been compiled into an updated guideline.

2.•• Kernan WN, Ovbiagele B, Black H, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke. 2014;45:2160–236.

This guideline provides the most up to date evidence based approach to patient management in the secondary prevention of stroke. However, additional evidence has surfaced as referenced in this review that has not yet been compiled into an updated guideline.

3.• Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370(26):2467–77.

This study is one of two important randomized controlled trials confirming a benefit of prolonged monitoring (30 days)

over 24 hour Holter monitoring and will likely be the basis for future guideline recommendations.

4.• Sanna T, Diener H-C, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370(26):2478–86.

This study is one of two important randomized controlled trials confirming a benefit of prolonged monitoring (up to 3 yrs) over 24 hour Holter monitoring and will likely be the basis for future guideline recommendations.

5. Committee ESOE, Committee EW. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008;25(5):457–507.
6. Sposato LA, Cipriano LE, Saposnik G, Vargas ER, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2015;14(4):377–87.
7. Holter NJ. New method for heart studies. Science (New York, NY). 1961;134(3486):1214–20.
8. Ritter MA, Kochhäuser S, Duning T, Reinke F, Pott C, Dechering DG, et al. Occult atrial fibrillation in cryptogenic stroke detection by 7-day electrocardiogram versus implantable cardiac monitors. Stroke. 2013;44(5):1449–52.
9. Gunalp M, Atalar E, Coskun F, Yilmaz A, Aksoyek S, Aksu NM, et al. Holter monitoring for 24 hours in patients with thromboembolic stroke and sinus rhythm diagnosed in the emergency department. Adv Ther. 2006;23(6):854–60.
10. Poli S, Diedler J, Härtig F, Götz N, Bauer A, Sachse T, et al. Insertable cardiac monitors after cryptogenic stroke—a risk factor based approach to enhance the detection rate for paroxysmal atrial fibrillation. Eur J Neurol. 2015.
11. Varounis C, Dagres N, Maounis T, Panagiotakos D, Cokkinos DV. Atrial premature complexes and heart rate have prognostic significance in 1-month atrial fibrillation recurrence after electrical cardioversion. Europace. 2007;9(8):633–7.
12. Wallmann D, Tüller D, Wustmann K, Meier P, Isenegger J, Arnold M, et al. Frequent atrial premature beats predict paroxysmal atrial fibrillation in stroke patients an opportunity for a new diagnostic strategy. Stroke. 2007;38(8):2292–4.
13. Binici Z, Intzilakis T, Nielsen OW, Køber L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation. 2010;121(17):1904–11.
14. Gaillard N, Deltour S, Vilotijevic B, Hornych A, Crozier S, Leger A, et al. Detection of paroxysmal atrial fibrillation with transtelephonic EKG in TIA or stroke patients. Neurology. 2010;74(21):1666–70.
15. Gladstone DJ, Dorian P, Spring M, Panzov V, Mamdani M, Healey JS, et al. Atrial premature beats predict atrial fibrillation in cryptogenic stroke results from the EMBRACE trial. Stroke. 2015;46(4):936–41.
16. Rosenberg MA, Samuel M, Thosani A, Zimetbaum PJ. Use of a noninvasive continuous monitoring device in the management of atrial fibrillation: a pilot study. Pacing Clin Electrophysiol. 2013;36(3):328–33.
17. Brachmann J, Morillo CA, Sanna T, Di Lazzaro V, Diener HC, Bernstein RA, et al. Uncovering atrial fibrillation beyond short-term monitoring in cryptogenic stroke patients: three-year results from the cryptogenic stroke and underlying atrial fibrillation trial. Circ Arrhythm Electrophysiol. 2016;9(1), e003333. doi:10.1161/circep.115.003333.
18. Tayal A, Tian M, Kelly K, Jones S, Wright D, Singh D, et al. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. Neurology. 2008;71(21):1696–701.
19. Miller DJ, Khan MA, Schultz LR, Simpson JR, Katramados AM, Russman AN, et al. Outpatient cardiac telemetry detects a high rate of atrial fibrillation in cryptogenic stroke. J Neurol Sci. 2013;324(1):57–61.
20. Sposato LA, Cipriano LE, Riccio PM, Hachinski V, Saposnik G. Very short paroxysms account for more than half of the cases of atrial fibrillation detected after stroke and TIA: a systematic review and meta-analysis. Int J Stroke. 2015;10(6):801–7. doi:10.1111/ijs.12555.
21. Khan M, Miller DJ, Schultz LR. Indecision in the clinical practice of anticoagulation for brief atrial arrhythmias after cryptogenic stroke. J Stroke Cerebrovasc Dis. 2013;22(8):e500–3. doi:10.1016/j.jstrokecerebrovasdis.2013.05.019.
22. Rothman SA, Laughlin JC, Seltzer J, Walia JS, Baman RI, Siouffi SY, et al. The diagnosis of cardiac arrhythmias: a prospective multi-center randomized study comparing mobile cardiac outpatient telemetry versus standard loop event monitoring. J Cardiovasc Electrophysiol. 2007;18(3):241–7.
23. Giada F, Bertaglia E, Reimers B, Noventa D, Raviele A. Current and emerging indications for implantable cardiac monitors. Pacing Clin Electrophysiol. 2012;35(9):1169–78.
24. Hindricks G, Pokushalov E, Urban L, Taborsky M, Kuck K-H, Lebedev D, et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation results of the XPECT trial. Circ Arrhythm Electrophysiol. 2010;3(2):141–7.
25. Podd SJ, Sugihara C, Furniss SS, Sulke N. Are implantable cardiac monitors the 'gold standard' for atrial fibrillation detection? a prospective randomized trial comparing atrial fibrillation monitoring using implantable cardiac monitors and DDDRP permanent pacemakers in post atrial fibrillation ablation patients. Europace. 2015. doi:10.1093/europace/euv367.

26. Christensen L, Krieger D, Højberg S, Pedersen O, Karlsen F, Jacobsen M, et al. Paroxysmal atrial fibrillation occurs often in cryptogenic ischaemic stroke. Final results from the SURPRISE study. Eur J Neurol. 2014;21(6):884–9.
27. http://www.mdbuyline.com/blog/for-conveniences-sake-medtronics-move-for-in-office-icm-procedures; Last accessed: January 2016.
28. https://clinicaltrials.gov/ct2/show/NCT02395536?term=NCT02395536&rank=1; Last accessed: January 2016.
29. Kanters TA, Wolff C, Boyson D, Kouakam C, Dinh T, Hakkaart L, et al. Cost comparison of two implantable cardiac monitors in two different settings: reveal XT in a catheterization laboratory vs. Reveal LINQ in a procedure room. Europace. 2015;2015, euv217.
30. Houmsse M, Ishola A, Daoud EG. Clinical utility of implantable loop recorders. Postgrad Med. 2014;126(2):30–7.
31. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, et al. Indications for the use of diagnostic implantable and external ECG loop recorders. Europace. 2009;11(5):671–87.
32. Rosero SZ, Kutyifa V, Olshansky B, Zareba W. Ambulatory ECG monitoring in atrial fibrillation management. Prog Cardiovasc Dis. 2013;56(2):143–52.
33. Afzal MR, Gunda S, Waheed S, Sehar N, Maybrook RJ, Dawn B, et al. Role of outpatient cardiac rhythm monitoring in cryptogenic stroke: a systematic review and meta-analysis. Pacing Clin Electrophysiol. 2015;38(10):1236–45.
34. Bernstein RA, Di Lazzaro V, Rymer MM, Passman RS, Brachmann J, Morillo CA, et al. Infarct topography and detection of atrial fibrillation in cryptogenic stroke: results from CRYSTAL AF. Cerebrovasc Dis. 2015;40(1–2):91–6.
35. Thijs VN, Brachmann J, Morillo CA, Passman RS, Sanna T, Bernstein RA, et al. Predictors for atrial fibrillation detection after cryptogenic stroke results from CRYSTAL AF. Neurology. 2015. doi:10.1212/WNL.0000000000002282.
36. Kamel H, Lees KR, Lyden PD, Teal PA, Shuaib A, Ali M, et al. Delayed detection of atrial fibrillation after ischemic stroke. J Stroke Cerebrovasc Dis. 2009;18(6):453–7.
37. Suissa L, Bertora D, Lachaud S, Mahagne MH. Score for the targeting of atrial fibrillation (STAF) a New approach to the detection of atrial fibrillation in the secondary prevention of ischemic stroke. Stroke. 2009;40(8):2866–8.
38. Alhadramy O, Jeerakathil TJ, Majumdar SR, Najjar E, Choy J, Saqqur M. Prevalence and predictors of paroxysmal atrial fibrillation on holter monitor in patients with stroke or transient ischemic attack. Stroke. 2010;41(11):2596–600.
39. Skaarup KG, Christensen H, Høst N, Mahmoud MM, Ovesen C, Olsen FJ, et al. Diagnosing paroxysmal atrial fibrillation in patients with ischemic strokes and transient ischemic attacks using echocardiographic measurements of left atrium function. Am J Cardiol. 2016;117(1):91–9.
40. Miller JD, Aronis KN, Chrispin J, Patil KD, Marine JE, Martin SS, et al. Obesity, exercise, obstructive sleep apnea, and modifiable atherosclerotic cardiovascular disease risk factors in atrial fibrillation. J Am Coll Cardiol. 2015;66(25):2899–906. doi:10.1016/j.jacc.2015.10.047.
41. Bhatt A, Majid A, Razak A, Kassab M, Hussain S, Safdar A. Predictors of occult paroxysmal atrial fibrillation in cryptogenic strokes detected by long-term noninvasive cardiac monitoring. Stroke research and treatment. 2011;2011.
42. Cotter PE, Martin PJ, Ring L, Warburton EA, Belham M, Pugh PJ. Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. Neurology. 2013;80(17):1546–50. doi:10.1212/WNL.0b013e31828f1828.
43. Horstmann S, Rizos T, Guntner J, Hug A, Jenetzky E, Krumsdorf U, et al. Does the STAF score help detect paroxysmal atrial fibrillation in acute stroke patients? Eur J Neurol. 2013;20(1):147–52. doi:10.1111/j.1468-1331.2012.03816.x.
44. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
45. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
46. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
47. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.
48. Pollack Jr CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373(6):511–20.
49. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373(25):2413–24.
50. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364(9):806–17. doi:10.1056/NEJMoa1007432.

51. Reddy VY, Mobius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). J Am Coll Cardiol. 2013;61(25):2551–6. doi:10.1016/j.jacc.2013.03.035.
52. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the watchman left atrial appendage system for embolic protection in patients with AF (PROTECT AF) clinical trial and the continued access registry. Circulation. 2011;123(4):417–24. doi:10.1161/circulationaha.110.976449.
53. Holmes Jr DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol. 2014;64(1):1–12. doi:10.1016/j.jacc.2014.04.029.
54. Srivastava MC, See VY, Dawood MY, Price MJ. A review of the LARIAT device: insights from the cumulative clinical experience. SpringerPlus. 2015;4:522. doi:10.1186/s40064-015-1289-8.