

Long-term Cardiac Monitoring for Detection of Occult Atrial Fibrillation – A Tool to Prevent Secondary Stroke in Cryptogenic Stroke Patients

Joerg Berrouschot

Head, Department of Neurology, Clinic Altenburger Land, Altenburg, Germany

Abstract

Stroke kills or disables millions of people every year. If the cause of a stroke is known, it is often possible to reduce the risk of a second stroke by appropriate patient management. However, up to a third of all ischaemic strokes remain cryptogenic, with no identified cause. Many of these strokes are suspected to be due to atrial fibrillation (AF), which is difficult to diagnose accurately. Small, leadless, insertable cardiac monitors (ICMs) gather data over three years, making them superior to other monitoring methods. The current review surveys the substantial supporting clinical data for the ICM Reveal XT, including the recently completed CRYSTAL-AF randomised clinical trial. The results consistently report previously undiagnosed AF in around 30 % of patients with cryptogenic stroke. ICM-provided data have direct consequences, as patients with AF-related stroke are indicated for protective oral anticoagulant therapies. Thus, ICMs will be important in the management of cryptogenic stroke, identifying and enabling patients with AF to receive life-saving therapies.

Keywords

Arrhythmias, insertable cardiac monitor, Reveal XT, anticoagulant therapy, stroke prevention

Disclosure: The author has no conflicts of interest to declare.

Received: 10 March 2014 **Accepted:** 28 April 2014 **Citation:** *European Neurological Review*, 2014;9(1):56–9

Correspondence: Joerg Berrouschot, Head, Department of Neurology, Clinic Altenburger Land, Am Waldessaum 10, D-04600 Altenburg, Germany. E: neurologie@klinikum-altenburgerland.de

Support: The publication of this article was supported by Medtronic. The views and opinions expressed are those of the author and not necessarily those of Medtronic.

Stroke remains a major killer worldwide, causing 5.7 million deaths in 2004 alone.¹ One in six people in the world will suffer a stroke in their lifetime: in Europe, stroke afflicts close to 10 million people.^{2,3} For survivors, stroke is disabling, with major negative effects on the quality of life of stroke victims and their family/carers.^{4–7} The substantial economic burden of post-stroke disability is of primary public health importance.

As a previous stroke is the greatest risk factor for a second stroke,⁸ it is imperative to diagnose the cause of a stroke accurately and provide patients with the most suitable preventive treatments possible. However, despite routine diagnostic evaluation, up to a third of all ischaemic strokes remain cryptogenic, with no identified cause.⁹ An improved understanding of the aetiology and more sensitive methods of screening for risk factors for cryptogenic stroke would greatly increase our ability to reduce rates of death and the suffering caused by the events.

Atrial Fibrillation and Cryptogenic Stroke

One of the most important and prevalent conditions detected in patients initially suspected of cryptogenic stroke is paroxysmal atrial fibrillation (PAF). AF is associated with increased morbidity and mortality from systemic thromboembolic complications, mainly affecting the cerebrovascular system.¹⁰ Thus, AF multiplies the risk of a stroke and also increases the severity of stroke compared with strokes not related to AF.^{11–13} The minimum atrial rate and duration that are thrombogenic are not known and hence it is not possible to set a lowest 'acceptable' degree of AF in patients post-ischaemic stroke.¹⁴

If PAF is documented in a stroke patient, this is an indication for oral anticoagulation, which can reduce the risk of further strokes by 50–70 %.¹⁵ Confirming suspected PAF in post-stroke patients is difficult, however, for two reasons. First, PAF episodes are intermittent and self-terminating and sporadic examinations are unlikely to identify them. Second, episodes of PAF are asymptomatic in as many as 50 % of patients, meaning these individuals are unlikely to seek care.¹⁶ Thus, there is significant underdiagnosis of PAF and as a consequence many patients do not receive the most effective treatment strategies. Stroke guidelines recommend aspirin to prevent recurrences in cases of unknown aetiology^{15,17} and, hence, oral anticoagulation therapies will be withheld from stroke patients with undiagnosed AF. Such inadequate protection markedly increases the risk of a secondary stroke in this population.

Most of the methods commonly employed to detect PAF show inadequate sensitivity to diagnose the condition. Although the diagnostic yield for detecting PAF is often highest soon after the stroke,¹⁴ it is well known that both single 24-hour Holter electrocardiogram (ECG) and traditional 2- to 3-day Holter monitoring have very low rates in detecting AF, revealing subclinical, or occult, AF in around 6 % of cases.^{14,18} A 30-day auto-triggered monitoring study revealed a PAF detection rate of 11 %.⁹ Increasing the duration of monitoring tends to increase the detection rates, with a yield of about 20 % for monitoring over 2 to 3 weeks.¹⁴

Two conclusions can be drawn from these numbers. First, undiagnosed AF is present in a significant number of patients, both stroke survivors

and in patients without a history of stroke but with cardiac conditions. Second, the true rates of occult AF in cryptogenic stroke patients remain unknown. Rates may be substantially higher than what has been reported from studies with short- and medium-term monitoring systems.

The fact that occult AF episodes are asymptomatic adds the further problem that the patient is not aware of anything abnormal. This increases the difficulty of motivating patients at risk to wear external monitors for the prolonged durations necessary to achieve adequate detection rates.¹⁹

The Role of Insertable Cardiac Monitors

In recent years the development of small, leadless, insertable cardiac monitors (ICMs) has provided physicians with a tool that could become a game changer in risk assessment of patients with cryptogenic stroke when an arrhythmic origin is suspected. After insertion in a short, minimally invasive outpatient procedure, ICMs have the capability to monitor continually for AF over a long time period. The most studied ICM is Reveal XT, which uses a dedicated AF detection algorithm to detect new-onset AF or recurrence of symptomatic or asymptomatic AF episodes during up to 3 years. Reveal XT has the capability of transmitting data over the telephone or wirelessly to the Internet, which enables physicians to review and evaluate the data on a secure computer connection.

Reveal XT is currently the only insertable leadless device able to detect AF with a validated algorithm. Two other ICMs are available – BioMonitor by Biotronik and SJMconfirm by St Jude Medical – but their clinical validation remains to be published.

In the Reveal XT Performance Trial (XPECT) in 247 patients, the performance of the ICM was compared with conventional Holter-ECGs obtained in parallel and evaluated by experts. In XPECT, the predefined Reveal XT algorithm had a sensitivity of 96.1 % and a specificity of 85.4 %. The negative predictive value was 97.4 %.²⁰ The accuracy of assessing the AF burden (the percentage of time patients were in AF) was 98 %.

These credentials indicate that validated ICMs such as Reveal XT may have an important role to play in monitoring patients with cryptogenic stroke for the presence of occult AF, which would ensure that these patients receive the most appropriate and protective therapies.

Observational Feasibility Studies with Reveal XT in Patients with Cryptogenic Stroke

A number of small-scale clinical trials have investigated the performance of Reveal XT in patients with cryptogenic stroke of suspected arrhythmic origin.

The largest population was included in an observational study conducted by Rojo-Martinez et al.²¹ A total of 101 patients who received a Reveal XT were included. The presence of AF was excluded by a number of methods including 12-lead ECG, continuous electrocardiographic monitoring in the stroke unit, transthoracic and transoesophageal echocardiogram and 24-hour Holter. The information provided by Reveal XT from each patient was reviewed online through the Medtronic Carelink network system.

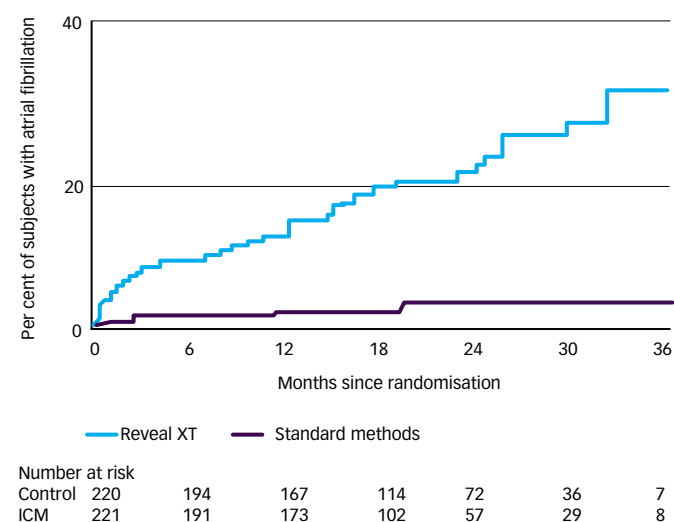
In this population, Reveal XT identified previously undetected AF in 33.7 %. The median (range) of monitoring prior to AF detection was 102 (26–240) days. The probability of detecting AF was greatest within the first 100 days after the ICM was implanted.

Table 1: Rates of Occult Atrial Fibrillation Detected by Reveal XT in Studies of Patients with Cryptogenic Stroke

Study Author and Reference	Number of Patients	Rate of Occult AF Detected by Reveal XT
Rojo-Martinez et al. ²¹	101	34 %
Ritter et al. ²²	60	17 %
Cotter et al. ²³	51	26 %
Etgen et al. ²⁴	22	27 %
Bernstein (CRYSTAL-AF) ²⁵	441	30 %

CRYSTAL-AF = CRYptogenic STroke and underlying Atrial Fibrillation.

Figure 1: Per Cent of Cryptogenic Stroke Patients with Atrial Fibrillation Identified with Reveal XT and Standard Monitoring Methods, Respectively, in CRYSTAL-AF



ICM = insertable cardiac monitor. Source: Adapted from Bernstein, 2014.²⁵

Stricter screening of candidates for Reveal XT was employed in an observational study conducted by Ritter and colleagues.²² Sixty patients received a Reveal XT within a median 13 days after an acute cryptogenic stroke event. The candidates were screened by 72-hour continuous rhythm monitoring on the stroke unit and only patients with negative findings received the ICM. After the ICM was implanted, 7-day Holter was performed as a comparative method for PAF detection.

In this rigorously screened population, Reveal XT identified an additional 10 cases of AF during follow-up. By contrast, the 7-day Holter analysis after implantation identified only three patients.

A notable finding was that there were no differences between patients with and without AF in terms of risk factors or risk scores. This underlines the difficulties in identifying patients at greatest risk of AF from clinical characterisations only.

Further support for the utility of Reveal XT were provided by a cohort study by Cotter et al.²³ in 51 stroke patients, all of whom had negative results for AF from rhythm monitoring with standard ECG and ≥24 hours of Holter monitoring. In this cohort, AF was detected by Reveal XT in 25.5 %. The median (range) of monitoring prior to AF detection was 48 (0–154) days.

Figure 2: Reveal XT and the Recently Launched Reveal LINQ, Side by Side for Size Comparison



A smaller population was included in an audit report by Etgen and co-workers,²⁴ who provided data on 22 patients who had received a Reveal XT and were followed for 12 months. All included patients had cryptogenic stroke confirmed by negative results from standard 12-lead ECG, 24–72-hour continuous stroke unit ECG monitoring and ≥ 1 additional 24-hour Holter-ECG. In this population, the rate of newly identified occult AF after 12 months was 27.3 %. The findings guided therapeutic decisions, as all patients with newly diagnosed AF were put on oral anticoagulation therapies.

These studies consistently confirmed the ability of Reveal XT to detect a significant percentage of occult AF in patients with cryptogenic stroke. Although the studies were small-scale, single-centre cohort studies of varying design, the rates of occult AF were similar in all populations (see *Table 1*).

After such pilot studies, larger, more rigorously designed clinical trials would be necessary to provide a solid foundation for the use of Reveal XT in stroke prevention. One such trial has recently concluded: the CRYPTogenic STroke and underlying Atrial Fibrillation (CRYSTAL AF) trial.²⁵

Randomised, Large-scale, Multicentre Study – CRYSTAL-AF

CRYSTAL-AF²⁵ was a randomised, multicentre, large-scale trial that compared Reveal XT with routine arrhythmia monitoring for identifying previously undetected AF in 441 patients with cryptogenic stroke. All included patients had a history of a cryptogenic stroke or transient ischaemic attack (TIA), confirmed in an examination using magnetic resonance imaging/computed tomography (MRI/CT), 12-lead ECG, 24-hour Holter, transesophageal echocardiography (TEE) or angiography.

One group of patients received Reveal XT, programmed to optimise AF detection. In the control group, cardiac monitoring was performed according to local standards for routine arrhythmia monitoring. AF episodes were identified by patients' physicians and adjudicated by an independent committee. AF was defined as an episode of irregular heart rhythm greater than 30 seconds.

The primary endpoint was detection of AF at 6 months. The results were strongly in favour of the use of Reveal XT: the detected rates of AF were 6.4 times greater with Reveal than with standard monitoring methods.

The differences between the groups increased with time: rates of AF identified by Reveal XT at 1 year was 12.4 % versus 2.0 % in the control arm and at 3 years the difference was even more striking: 30 % AF identified with Reveal XT compared with 3 % using routine monitoring methods (see *Figure 1*).

The treating physicians adhered closely to guidelines for stroke prevention: >95 % of patients with identified AF in both groups were put on oral anticoagulant therapies. In consequence, the use of Reveal XT was associated with a dramatic increase in the proportion of stroke patients receiving protective oral anticoagulants: at 12 months, 14.7 % of patients in the Reveal XT group and 6.0 % of patients in the control group were on anticoagulants. (No data were presented from the 3-year analysis.)

Since the patient characteristics in CRYSTAL-AF were similar in both treatment groups, it is clear that the greater rates of AF detected in the Reveal XT group and the associated increase in the use of protective oral anticoagulants were due to the use of the ICM.

Outlook

Stroke is one of the most devastating vascular events to both the victims of the event and to their social environment. The recent developments discussed above provide hope for improved management of cryptogenic stroke patients. Looking ahead, a couple of conclusions and predictions can be made with reasonable confidence.

First, ICMs will have an important role in preventing recurrent events in patients with cryptogenic stroke. It is clear that the median time to the first AF episode is significantly longer than the 24–72 hours commonly used in Holter monitoring of stroke patients. Such long-term data are only available with ICMs. The clinical consequences are clear: in the studies discussed, many patients with AF-related stroke were put on protective oral anticoagulants as a direct consequence of ICM-provided data. This is in accordance with clinical guidelines. But without the data from Reveal XT, these patients would have been labelled 'cryptogenic' and put on aspirin, also in accordance with guidelines.

Second, AF is common but not universal in patients with cryptogenic stroke. This justifies the use of ICMs. With rates around 30 %, the number of eligible patients detected using ICMs justifies a minimal invasive insertion. With rates close to 100 % a general use of anticoagulants would have been warranted. Conversely, very low rates would not have justified use of the ICM. With the arrival of new, further miniaturised ICMs such as the recently launched Reveal LINQ, the procedural and economic barriers to uptake of these important tools will be reduced even further. At only around 1 cm³, one-third the volume of a AAA battery, Reveal LINQ is up to 80 % smaller than other ICMs (see *Figure 2*).

Although promising, there are limitations to the available ICM studies. The finding of AF in patients with cryptogenic stroke is not in itself evidence of causation. Reduction in stroke rates with Reveal-guided management would need to be demonstrated conclusively. Rates of recurrent stroke in the different treatment groups were not a predefined endpoint in CRYSTAL-AF.

Still, it seems highly appropriate to conclude, like the CRYSTAL-AF investigators did at their presentation of the results in 2014: "Long-term continuous monitoring should be performed in patients with cryptogenic stroke." ■

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