CRYPTOGENIC STROKE: EXPERT OPINION ON ATRIAL FIBRILLATION MONITORING AND RISK MANAGEMENT

Proceedings from the Stroke Day symposium at Milan Malpensa.
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CONTENTS

INTRODUCTION

Stroke accounts for >10% of total deaths worldwide (2010 figures), making it the second largest cause of death globally after heart disease.[1] As stroke survivors are at enhanced risk for a second stroke,[2] prevention of recurrences is the main objective of long-term management. However, a substantial percentage of strokes are categorised as cryptogenic, events for which extensive investigation does not identify a cause. This makes it difficult to treat patients to reduce the risk of sequelae.

It is well known that undiagnosed atrial fibrillation (AF) is present in up to 30% of cryptogenic stroke survivors, and since AF is a powerful risk factor for recurrent stroke these patients might benefit from oral anticoagulation therapies. However, as cryptogenic stroke falls into the specialities of both neurology and cardiology, interdisciplinary collaboration is needed to characterise and treat stroke survivors.

Current guidelines in Europe and the US recommend prolonged ECG monitoring for AF in survivors of an ischaemic stroke without diagnosed AF.[3,4] While this recognises the importance of identifying hidden AF, there are few specific recommendations on the most appropriate methods to use, or on the duration of monitoring in patients with different characteristics. Moreover, efficient management and analysis of the information generated by monitoring technologies requires a well organised system to manage the data flow and timely sharing of relevant information between neurologists and cardiologists. Finally, findings need to be tied to clear actions. This means agreeing on what findings should trigger the decision to prescribe oral anticoagulation.

With the objective to identify consensus opinions on various important questions around cryptogenic stroke management, a group of European expert neurologists and cardiologists gathered for an interdisciplinary meeting in Milan, Italy in November 2016. This communication presents the main outcomes and recommendations that emerged from the group discussions.

SCOPE OF THE PROBLEM: THE IMPORTANCE OF CRYPTOGENIC STROKE

Around a third of all ischaemic strokes or transient ischaemic attacks (TIA) are labelled as cryptogenic, indicating an unknown origin. In Europe this corresponds to around 400,000 cases every year.[5]

In contrast to other variants of stroke/TIA, the diagnosis of cryptogenic stroke/TIA is not made by identifying typical signs and symptoms, but by eliminating all other potential causes.[6] The importance of cryptogenic stroke is further demonstrated by the fact that a high percentage of second strokes after a cryptogenic event remain diagnosed as cryptogenic *(Figure 1)*.

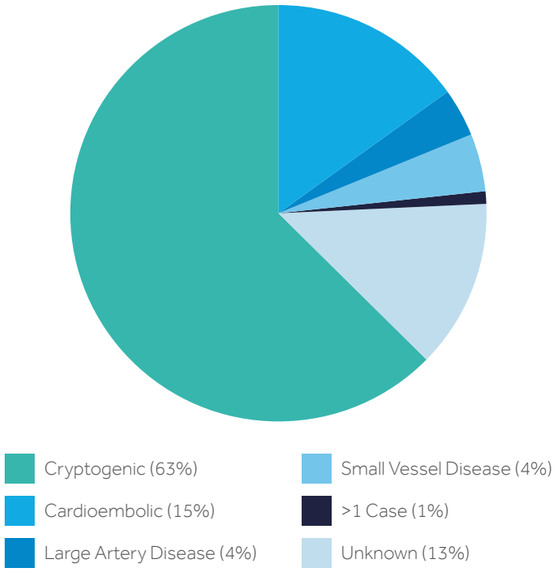

Figure 1. Causes of second stroke after a first cryptogenic stroke.[7]

Current cryptogenic stroke management is mostly based on antiplatelet therapy, together with attempts to reduce risk factors for recurrent stroke.[3] However, antiplatelet therapy will not provide adequate protection for patients with undiagnosed AF. Those patients would need oral anticoagulants.[8]

A large part of cryptogenic strokes may now be included in the recently proposed category of Embolic Strokes of Undetermined Source (ESUS). ESUS describes "a non-lacunar ischaemic stroke without a defined cause" *(Table 1)*.[9] The definition represents a step towards a unified diagnosis but there is a definite need for standardised diagnostic procedures for cryptogenic stroke patients. At the Expert Meeting, cryptogenic stroke was defined according to the TOAST criteria.[10] In addition there was consensus that lacunar strokes without identified aetiological factors such as hypertension, diabetes mellitus or white matter lesions should be classified as cryptogenic.

The Expert panel emphasised that while physicians and researchers have an interest in finding a cause for cryptogenic stroke and ESUS, the first priority to patients is to reduce the risk of future events. For this, to identify and counter manageable risk factors may be more important than finding the cause of the original stroke. Among such manageable risk factors the most important is AF.

To reduce the risk of future events should be the first priority in cryptogenic stroke management.

DEFINITION OF ESUS

Non-lacunar infarct (subcortical infarct ≤1.5 cm on CT or ≤2.0 cm on MRI)

Absence of:

- Extracranial or intracranial atherosclerosis causing >50% luminal stenosis in the artery supplying the ischaemic region
- Major cardioembolic sources (AF, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, myocardial infarction within the past 4 weeks, left ventricular ejection fraction <30%, valvular vegetations or infective endocarditis)
- Other specific cause of stroke (e.g., dissection, arteritis, migraine/ vasospasm, drug misuse)

Table 1. Definition of ESUS.[11]

THE ROLE OF AF IN STROKE

The importance of AF as a risk factor for stroke is well established.[4] Patients who suffer a cardioembolic stroke and have AF are at increased risk of further strokes and other adverse outcomes compared with similar patients without AF.[12] Additionally, strokes in patients with AF are often more severe than other strokes *(Figure 2)*.[13,14] Thus, to prevent AF-associated strokes means to prevent the worst strokes.

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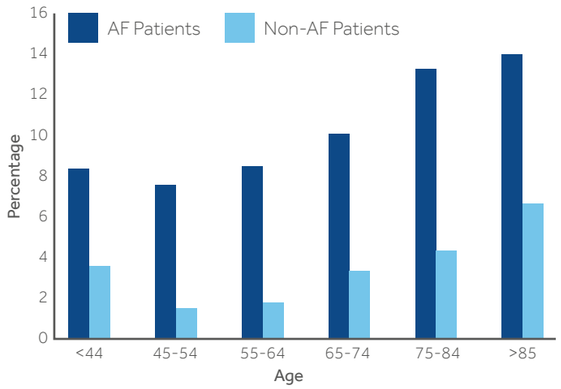

Figure 2. Deaths within 28 days of admission for stroke in patients with and without AF, respectively, in different age groups. From Kimura et al.[14]

Contemporary studies show that AF is diagnosed (before, during or after the initial event) in 20–30% of patients with an ischaemic stroke.[15–17] The CRYSTAL-AF and EMBRACE studies, using different electrocardiographic (ECG) monitoring methods, identified paroxysmal AF in up to one-third of patients with cryptogenic stroke/TIA.[18,19] Several studies have also found AF in patients in whom another competing cause for stroke was identified clinically (e.g. hypertension or carotid artery stenosis).[20,21]

The harm associated with AF in stroke creates a substantial financial burden: data from Denmark indicate that the average 3-year costs attributable to stroke in a patient with AF corresponded to US $30,925, of which two thirds were healthcare costs. From the second year after the stroke, costs of social care services exceeded health care costs.[22]

Recent data from Europe and the US indicate that rates of AF in patients admitted to hospital may be increasing.[13,23] Although it is likely that part of the increase is due to improved AF detection, the data highlight the risk and need for appropriate prevention strategies in patients with suspected AF.

WHICH METHODS SHOULD BE USED TO MONITOR CRYPTOGENIC STROKE PATIENTS FOR AF?

Patients admitted for an acute stroke are routinely screened for AF with 24-hr Holter monitoring or 72-hr continuous telemetry. However, these methods are not sufficiently sensitive for the detection of paroxysmal AF.[17,24] It is clear from a number of recent studies that the longer patients are monitored, the greater the detection rates of AF *(Figure 3)*.[18,19] Confirming the high rates of AF and its importance as an actionable risk factor for stroke, current ESC and AHA guidelines recommend prolonged rhythm monitoring (30 days) for AF as reasonable within 6 months of the index event[3] or "for 72 h after a stroke, or even longer periods".[4]

Consensus among the Experts was that "the more you look, the more you find." Repeated 24-hr Holter may detect more AF than single Holter, but still has low sensitivity. Ambulatory ECG monitoring for 30 days has much greater ability to detect AF.[25] Insertable cardiac monitors (ICMs) have the greatest sensitivity[26] and were the method of choice in cryptogenic stroke patients for the majority of the Experts at the meeting.

Insertable cardiac monitors have the greatest sensitivity for AF detection and are many experts' method of choice in cryptogenic stroke patients.

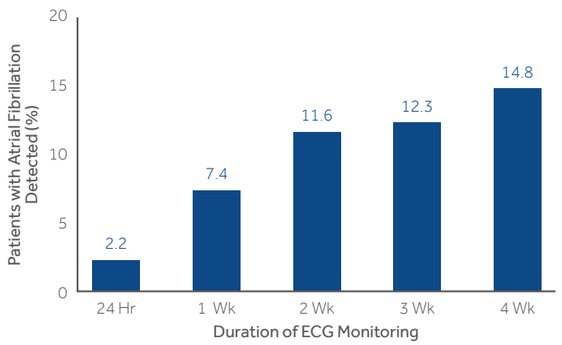

Figure 3. 'The more you look the more you find'. Increasing rates of AF detection with prolonged monitoring.[25]

The CRYSTAL-AF trial compared AF detection rates with ICM and standard monitoring methods in cryptogenic stroke survivors. At 6 months ICM monitoring detected AF in 8.9% of patients (versus 1.4% in patients monitored by routine methods). Detection rates increased with time, to 12.4% at 12 months and 30% at 3 years (versus 3% using standard monitoring methods; *Figure 4*).[18]

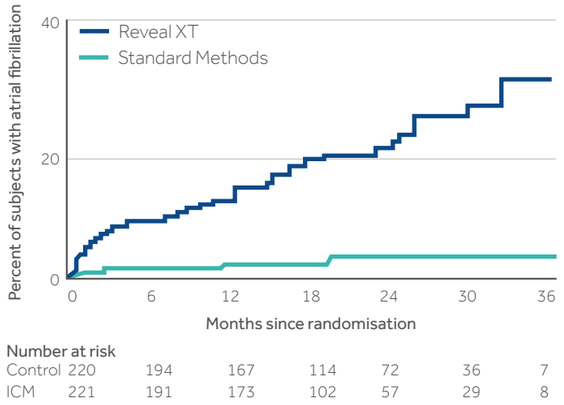

Figure 4. 'Per cent of cryptogenic stroke patients with AF identified with ICM (Reveal XT) and standard monitoring methods, respectively, in CRYSTAL-AF. Adapted from reference.[27]

The continuously collected data from ICM in CRYSTAL-AF have been used in a sub-analysis to estimate the potential to detect AF with various monitoring methods and duration. By selecting data only at specific time points it was possible to mimic the performance of other monitoring systems such as external monitors. In the simulation, which modelled detection rates over a minimum follow-up duration of 345 days, single 24-hr Holter detected only 1.3% as many AF occurrences as the ICM.[26] Even the most successful alternative, 30-day monitoring, detected only 23% as many events as the ICM, similar to four quarterly 7-day Holter monitoring periods (and much better than 12 monthly 24-hr Holter monitoring episodes *(Figure 5)*. This indicates that >75% of patients with AF may be lost with external monitoring ≤30 days. As the simulation assumed that patients wore their monitors with 100% compliance, the estimates are probably conservative compared with actual care.

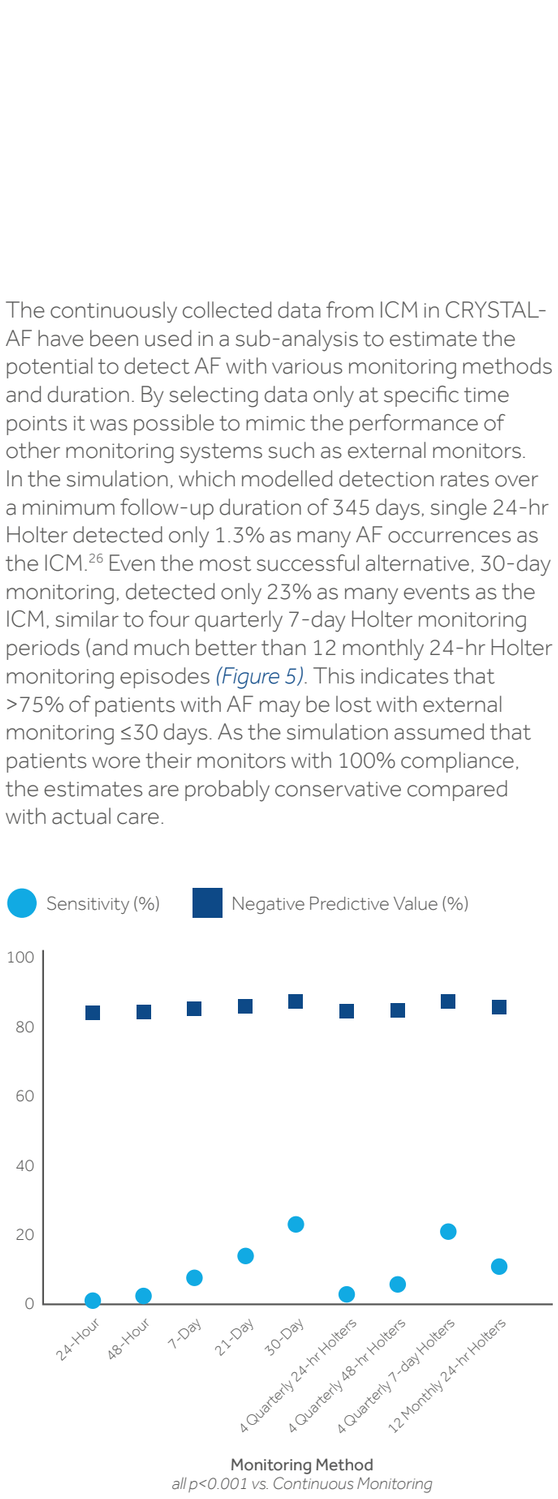

Figure 5. 'Simulated sensitivity and negative predictive value of different monitoring options for the detection of AF in patients after a cryptogenic stroke. The ICM sensitivity was set to 100% and all modelling simulated 345 days follow-up.[26]

In the experts' unanimous opinion, 30 days of monitoring without detecting AF is not enough to decide if a cryptogenic stroke patient has AF. Most participants recommended long-term monitoring with ICM in these patients.

The Experts noted that monitoring TIA patients may be equally valuable to monitoring patients with stroke, since they have suffered less neurological damage than stroke patients and may have more to gain than stroke sufferers from protection against a subsequent event.

30 days of monitoring without detecting AF is not enough to decide if a cryptogenic stroke patient has AF.

EXPERT OPINION

With AF, "the more you look, the more you find."

For all strokes, current ESC and AHA guidelines recommend prolonged rhythm monitoring (30 days) for AF within 6 months of the index event.

In patients with cryptogenic stroke 30 days of monitoring without detecting AF is not enough to decide if a cryptogenic stroke patient has AF.

ESC guidelines state that continuing monitoring with ICM should be considered in these patients.

Monitoring TIA patients may be equally valuable to monitoring patients with stroke.

WHICH PATIENTS WITH CRYPTOGENIC STROKE SHOULD BE MONITORED FOR AF WITH ICMS?

Current ESC guidelines state that in stroke survivors, "additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered" to document silent AF (recommendation class IIa, level of evidence B).[4] The Experts emphasised that most cryptogenic stroke patients would benefit from prolonged monitoring.

In actual care, financial considerations pushes physicians towards using ICMs preferentially in those patients with the greatest likelihood for undiagnosed AF. The question of the most suitable population for monitoring has not been adequately settled at present, but some general guiding recommendations were made at the Expert meeting *(Figure 6)*.

A number of predictors of increased risk of AF have been identified in clinical studies, most prominently older age and an evidence of prior cortical or cerebellar infarcts.[28,29] In the Experts opinion, however, younger patients may also be at a relevant risk for AF although routine monitoring cannot be generally recommended in this population.

Among cardiac factors, a dilated left atrium is associated with risk of new-onset AF[30,31] and non-AF atrial arrhythmias such as premature atrial contractions or short atrial runs also indicate a predisposition to AF.[32–34] Data are needed to support anticoagulation based on these abnormalities without identified AF[32] and currently they are mostly valuable as predictors of risk for AF.

Most cryptogenic stroke patients would benefit from prolonged monitoring for the presence of AF.

Use of the CHA_2DS_2-VASc risk score is recommended by the ESC guidelines for patient stratification in AF.[4] The group most likely to benefit from identifying and acting on the presence of AF are those at intermediate risk. Many patients with cryptogenic stroke would fall into this category since previous stroke or TIA is among the most important factors in the CHA_2DS_2-VASc score *(Table 2)*.

A high CHA_2DS_2-VASc score suggests that the risk of stroke or thromboembolism is high even in the absence of AF.[35,36] Whether anticoagulation without attempts to identify AF would be an option in these patients is investigated in on-going clinical studies (RE-SPECT ESUS, NCT02239120; NAVIGATE ESUS, NCT02313909; ATTICUS, NCT02427126).
The potential disadvantage is that it might represent a one-size-fits-all approach to stroke management, while we do not know whether all patients will benefit from the same treatment, irrespective of aetiology or risk profile.

CHA_2DS_2-VASC RISK FACTOR	POINTS
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Previous stroke, TIA or thromboembolism	2
Vascular disease (myocardial infarction, peripheral artery disease, aortic plaque)	1
Age 65-74 years	1
Female sex	1

Table 2. CHA_2DS_2-VASc risk factors.[37]

EXPERT OPINION
Most cryptogenic stroke patients would benefit from prolonged monitoring.

Although age is a predictor of increased risk of AF, younger patients may also be at a relevant risk for AF although routine monitoring cannot be generally recommended in this population.

Important surrogates for AF are dilated left atrium and non-AF atrial arrhythmias such as atrial premature beats or short atrial runs.

The group most likely to benefit from identifying and acting on the presence of AF are those with intermediate CHA2DS2-VASc risk scores.
This includes most cryptogenic stroke patients.

PHASE 1 EMERGENCY ROOM	**PHASE 2** IN HOSPITAL STAY	**PHASE 3** FIRST AMBULARORY PERIOD	**PHASE 4** SECOND AMBULARORY PERIOD
▪ Admission ECG *(with no history of AF)*	▪ Serial ECG ▪ Continuous inpatient ECG monitoring ▪ Continuous cardiac telemetry ▪ In-hospital Holter monitoring	▪ Ambulatory Holter Monitoring	▪ Mobile cardiac outpatient telementry ▪ External loop recording ▪ Implantable loop recordning
Post stroke AF diagnosis **7.7%**	Post stroke AF diagnosis **5.1%**	Post stroke AF diagnosis **10.7%**	Post stroke AF diagnosis **16.9%**

Figure 6. Sequential cardiac monitoring model and diagnostic yield in each phase based on a meta-analysis (50 studies comprising 11.658 post-stroke patients). Adapted from Sposato et al,[38]

HOW SHOULD DATA MANAGEMENT AND INTERPRETATION BE ORGANISED?

Proper management, prioritisation and analysis of data is critical for physicians and other healthcare providers.

The organisation of data management is a relevant problem with all insertable cardiac monitoring devices. The amount of data will increase in the future with the growth in the number of devices capable of transmitting and storing biological information. To make the most out of this information, a structured prioritisation and analysis of data is critical.

Successful current solutions to the problem have involved setting up a central initial point for handling the flow of data from patients monitored for AF with ICMs. Often this role is allocated to a nurse or technician in the cardiology department.
The responsible individual reviews all incoming data and forwards relevant information to the neurologist and cardiologist. Cardiologists need to be closely involved at the interpretation stage, to ensure all potential arrhythmias are identified and no artefacts are misinterpreted. Working as a multidisciplinary team, the experts translate the information into action as necessary. In particular, in patients with AF diagnosed on ICM data, the decision to start oral anticoagulation should be taken jointly by neurologists and cardiologists.

Regardless of speciality, there was consensus among the Experts that physicians would only need notifications when AF is detected in a patient; there is no need for regular reports of absence of arrhythmias. However, decisions and actions need to be taken rapidly. Consensus among cardiologists was that it is highly important to receive information about an AF episode in a cryptogenic stroke patient within a day. In most cases, it will not be necessary to involve the general practitioner, although a line of communication should be available for ad-hoc needs.

When discussing communications it is important not to forget the patient. The interdisciplinary team that shares information among its members will need to include the patient at appropriate times on a case-to-case basis. This role may be best allocated to nurses. This group of professionals would also represent an important resource for patient education. This would ensure that patients gain an understanding of ICM insertion procedures, the CareLink concept of data transfer between device and clinic *(Figure 7)*, as well as the installation and use of data transfer components in the home.

EXPERT OPINION
A specialised nurse or technician is recommended as central initial point for ICM data review.

Relevant information should be forwarded to the stroke neurologist and cardiologist.

Cardiologists need to be closely involved in ICM data interpretation, to ensure all potential arrhythmias are identified and no artefacts are misinterpreted.

It is important that information about an AF episode in a cryptogenic stroke patient is communicated to neurologists and cardiologists with minimal delay.

Working as a multidisciplinary team, the experts translate the information into action as necessary.

In patients with AF diagnosed on ICM data, the decision to start anticoagulation should be taken jointly by neurologists and cardiologists.

HOW REMOTE MONITORING WORKS

1. INSERT
...the Reveal LINQ™ ICM.

2. ENROL
... patient into CareLink™ network.

3. TRANSMIT
... data wirelessly from Reveal LINQ™ to secured server.

4. REVIEW
...data via clinician website.

Figure 7. Schematic representation of the CareLink™ system for data transfer between ICM and healthcare professional.

WHAT FINDINGS SHOULD TRIGGER ANTICOAGULATION?

It is well demonstrated that oral anticoagulation reduces stroke and mortality in patients with AF.[39,40] What remains unknown is what level of AF should trigger treatment and what can be considered a "safe" level. There may be low levels of AF in which anticoagulation may not be protective and may increase other risks to patients. This is an important issue, particularly when AF is identified with highly sensitive methods such as ICMs, over a long time period.

Oral anticoagulation reduces stroke and mortality in patients with AF

Studies in primary prevention patients have suggested that AF episodes lasting 5-6 minutes or more are associated with an increased risk of ischaemic stroke.[41,42] A large majority (90%) of the Experts agreed that cryptogenic stroke patients with episodes lasting at least 5 minutes should be started on anticoagulation therapy based on these findings. Whether shorter duration of episodes should indicate anticoagulation cannot be settled without further data. It was pointed out that no studies have been conducted to demonstrate whether oral anticoagulation reduces the risk of stroke in patients with AF episodes <6 min. The Experts were evenly divided on the question whether anticoagulation should be provided to patients with AF episodes >30 seconds. Shorter periods were not considered an indication for anticoagulation.

EXPERT OPINION
Patients with AF episodes lasting 5-6 minutes or more should be started on anticoagulation therapy.

Episodes >30 seconds up to 5 minutes remain an unsolved question and should be left to physicians' discretion in individual cases.

AF episodes <30 seconds should not be considered an indication for anticoagulation.

OTHER CONSIDERATIONS

A survey at the Expert Meeting highlighted a number of other discrepancies and needs among neurologists and cardiologists specialising in stroke management. Among the most important outstanding needs were:

Greater interaction between neurologists and cardiologists: The degree of interaction between cardiologists and neurologists varies greatly between individual hospitals. Around half of the expert neurologists reported an established institutionalised relationship with cardiologists. A quarter of neurologists never consulted cardiologists for identification of cryptogenic stroke/TIA.

Consistent standard operating procedures and definitions of cryptogenic strokes: Less than 20% of hospitals had standard procedures for stroke diagnosis and in approximately half of hospitals the definition varied with the diagnosing physician's experience. This lack of unity was reported equally by neurologists and cardiologists. The panel strongly recommended to establish diagnostic standard operating procedures in hospitals.

Multidisciplinary collaboration on the establishment of stroke care pathways: The process of establishing stroke care pathways is often driven by one speciality more than the other. The Experts recommended cardiologists and neurologist to work closer on this task.

Greater clarity on whether to explant the ICM when AF is diagnosed: Currently ICMs are often explanted once AF has been detected. However, cardiologists would recommend to leave the device in place until the end of the battery life, typically 3 years. The device may be useful to detect other arrhythmias after AF detection and help guide efforts at rhythm and rate control of AF. No clear recommendations on explants are available at present.

CONCLUSIONS

Stroke is a dramatic neurological event with a number of cardiac predisposing factors. This calls for a multidisciplinary diagnostic workup and management of stroke patients. Although it would be highly valuable to identify causes of cryptogenic stroke, what matters to the patient is to receive maximal protection from subsequent events. In the diagnostic work-up, the presence of AF is an actionable finding. The development of ICMs has greatly boosted the ability to identify arrhythmias over the long term, increasing the chances that patients with undiagnosed AF will be identified and receive protective anticoagulants.

Although the ICM is primarily a cardiological diagnostic tool, decisions based on its findings need to be taken in close collaboration between neurologists and cardiologists. Moreover, to optimise the value of data generated by implantable devices standardised procedures and clear lines of communication will be necessary. Such interconnected multidisciplinary teams will be well positioned to take advantage of current and future technological developments to improve cryptogenic stroke patient care.

ACKNOWLEDGEMENTS

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Table 3.

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BRIEF STATEMENT
See the device manual for detailed information regarding the instructions for use, [the implant procedure], indications, contraindications, warnings, precautions, and potential adverse events. For further information, contact your local Medtronic representative or consult the Medtronic website at www.medtronic.com.

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