Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke: a systematic review and economic evaluation

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Scientific summary

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Background

Up to one-third of first strokes are termed cryptogenic strokes because no known cause is identified. Atrial fibrillation is a common arrhythmia associated with a fivefold increased risk of stroke. Patients who have had a stroke are investigated for atrial fibrillation, although it can be intermittent and asymptomatic, and so may be undetected by standard post-stroke investigations. Implantable cardiac monitors are small devices inserted under local anaesthetic via a small incision in the chest that capture and transmit electrocardiograms over a period of up to 4 years. The devices vary in size, cost, battery life, programming of parameters to detect arrhythmias and the way data are transmitted and reviewed by clinicians; however, if they detect atrial fibrillation, a patient's risk of subsequent stroke can be reduced by changing their antiplatelet therapy to an oral anticoagulant.

Objectives

The objectives were to assess the clinical effectiveness and cost-effectiveness of the BioMonitor 2-AF™ (Biotronik SE & Co. KG, Berlin, Germany), the Confirm Rx™ (Abbott Laboratories, Lake Bluff, IL,USA), and the Reveal LINQ™ (Medtronic plc, Minneapolis, MN, USA) implantable cardiac monitors to detect suspected paroxysmal atrial fibrillation in people who have had a cryptogenic stroke. The review considered the diagnostic accuracy, clinical effectiveness and cost-effectiveness of the three implantable cardiac monitors compared with no further testing after at least 24 hours of outpatient external ambulatory electrocardiography.

Methods

Clinical effectiveness methods

A systematic review was conducted to identify diagnostic test accuracy and clinical effectiveness studies on the use of the implantable cardiac monitors and their earlier models. The comparators were each of the implantable cardiac monitors versus each other or versus no further testing after outpatient external ambulatory electrocardiographic monitoring. Electronic database searches in MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects and the Health Technology Assessment database were conducted in September 2018. A single randomised controlled trial, Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL-AF) (Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, *et al.* Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478–86), assessing an earlier Medtronic Reveal model (XT rather than LINQ) met the eligibility criteria, so the criteria were widened to find evidence for the BioMonitor 2-AF, Confirm Rx and Reveal LINQ. First, non-comparative observational studies were sought within the cryptogenic stroke population, and then evidence was considered from studies of mixed populations submitted by each company. Only the CRYSTAL-AF trial fell within the eligibility criteria outlined in the original published protocol for this Diagnostic Assessment Report, so the additional evidence should be interpreted with caution. It should also be noted that atrial fibrillation detection rates in implantable cardiac monitor devices are dependent on the patient population, as is the incidence of the other clinical outcomes of interest in this Diagnostic Assessment Report. The results from non-cryptogenic stroke populations may not be representative of the implantable cardiac monitor device performance in cryptogenic stroke patients.

The titles and abstracts of all identified studies from the electronic database searches were independently assessed for inclusion by two reviewers. The Cochrane Risk of Bias 2.0 tool was used for quality assessment of the randomised controlled trial and extracted data were validated by a second reviewer. There were insufficient clinically and methodologically homogenous data available to enable data to be pooled and meta-analysed; therefore, data from the randomised controlled trial, observational cryptogenic stroke studies and mixed population studies were tabulated and discussed narratively.

Cost-effectiveness methods

A systematic review was performed to identify published economic evaluations of implantable cardiac monitors for the detection of atrial fibrillation in a cryptogenic stroke population. Electronic database searches in MEDLINE, MEDLINE Ahead of Print, MEDLINE In-Process, EMBASE, EconLit, NHS Economic Evaluation Database, Cochrane Database of Systematic Reviews, Cochrane Central Database of Controlled Trials, Database of Abstracts of Reviews of Effects and Health Technology Assessment database were conducted in September 2018. Additional searches were carried out in September 2018 to identify data on relevant costs and health-state utilities.

A two-stage de novo economic model was developed to assess the cost-effectiveness of Reveal LINQ, BioMonitor 2-AF and Confirm Rx compared with standard of care monitoring to detect atrial fibrillation in patients who have had a cryptogenic stroke. The first stage of the model, developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) was a short-term patient flow model to estimate the number of cryptogenic stroke patients who would have atrial fibrillation detected by either an implantable cardiac monitor or standard of care monitoring. Detection of atrial fibrillation determines whether or not patients start anticoagulation treatment for atrial fibrillation, instead of remaining on antiplatelet treatment for cryptogenic stroke. The second stage of the model, developed using R statistical software (The R Foundation for Statistical Computing, Vienna, Austria), was a long-term Markov model that captured the lifetime costs and benefits of patients on either anticoagulation or antiplatelet treatment. Data on atrial fibrillation detection rates for all three implantable cardiac monitors are based on results from the CRYSTAL-AF trial. A probabilistic sensitivity analysis was conducted to establish the level of uncertainty in the model parameters. In addition, a deterministic one-way sensitivity analysis and various scenario analyses were performed to assess the uncertainty in the assumptions used in the model. Total costs and quality-adjusted life-years, as well as incremental costs and quality-adjusted life-years and incremental cost-effectiveness ratios, are reported. Costs and outcomes over the lifetime horizon were discounted at an annual rate of 3.5%.

Results

Summary of clinical effectiveness results

No diagnostic test accuracy studies were identified exclusively in the cryptogenic stroke population, irrespective of the comparator selected, and only one randomised controlled trial was identified in a cryptogenic stroke population (CRYSTAL-AF, $n = 441$). The CRYSTAL-AF trial was an open-label randomised controlled trial that compared the Reveal XT with conventional follow-up.

Twenty-six single-arm observational studies were identified after widening the eligibility criteria to include non-comparative studies. The studies all assessed the Reveal XT and Reveal LINQ; none provided evidence suitable to assess the efficacy of BioMonitor 2-AF or Confirm Rx. Therefore, one study for Confirm DM2102 (Abbott Laboratories), five studies of the BioMonitor 2 (Biotronik SE & Co. KG) and five studies of the Reveal LINQ or XT in mixed populations were included from company submissions. The mixed population studies were all single-arm observational studies or diagnostic test accuracy studies using Holter monitoring as the reference standard.

Atrial fibrillation detection in the CRYSTAL-AF trial was higher with the Reveal XT than conventional follow-up at all time points; by 36 months, atrial fibrillation was detected in 19% of implantable cardiac monitor patients, compared with 2.3% of those receiving conventional follow-up. Median time to atrial fibrillation detection was longer with the implantable cardiac monitor than with conventional follow-up (36 months), but the rate of atrial fibrillation detection was significantly higher with the Reveal XT than with conventional follow-up (hazard ratio 8.8, 95% confidence interval 3.5 to 22.2; $p < 0.001$) and > 90% of patients diagnosed with atrial fibrillation in the implantable cardiac monitor arm started an oral anticoagulant. The observational studies demonstrated that, even within a cryptogenic stroke population, atrial fibrillation detection rates are highly variable, but results were broadly consistent with the CRYSTAL-AF trial.

In the CRYSTAL-AF trial, recurrent stroke or transient ischaemic attack rates were 5.0% with an implantable cardiac monitor versus 8.2% with conventional follow-up at 6 months, 6.8% versus 8.6%, respectively, at 12 months and 9.0% versus 10.9%, respectively, at 36 months (all $p > 0.05$). EuroQol-5 Dimensions scores (confidential information has been removed).

Device-related adverse events, such as pain and infection, were low in the CRYSTAL-AF trial, the single-arm observational studies and the mixed population studies. In the CRYSTAL-AF trial, the rate of serious adverse events was similar between groups (around 25–30%), but more implantable cardiac monitor patients had non-serious adverse events than those receiving conventional follow-up (18.6% vs. 4.1%, respectively). At 12 months' follow-up, 3.4% of implantable cardiac monitors had been removed in the CRYSTAL-AF trial.

The results of the mixed population studies suggest that enhancements over time to the atrial fibrillation diagnosis algorithm in the Reveal implantable cardiac monitors has improved their diagnostic test accuracy. A naive comparison of the mixed population diagnostic test accuracy studies of the Confirm DM2102 and Reveal LINQ suggests that they both have 100% sensitivity for atrial fibrillation detection, although specificity varies (85.7% and 99.0%, respectively). The BioMonitor 2 (confidential information has been removed). However, this comparison is subject to clinical heterogeneity (patient populations, interventions and study designs) and the data are not necessarily reflective of cryptogenic stroke patients or the implantable cardiac monitor models of interest.

Summary of cost-effectiveness results

One study was identified that assessed the cost-effectiveness of the Reveal XT implantable cardiac monitor (a predecessor of the Reveal LINQ) compared with standard of care monitoring in a cryptogenic stroke population. The economic evaluation was reviewed to determine the viability of using the model for the purposes of this Diagnostic Assessment Report, but it was considered that the results produced by the model are potentially unreliable, as there is significant uncertainty and potential flaws in the estimation of the clinical parameters in the model, particularly around the estimation of treatment effects by indirect comparison, atrial fibrillation incidence and detection rates used in the analysis.

However, the initial health states of the Reveal XT model to determine atrial fibrillation status were considered appropriate to inform a de novo short-term model, in which the time horizon is linked to the battery life of an implantable cardiac monitor device. From the short-term model, patients with atrial fibrillation (whether detected or undetected) would then feed into a long-term (lifetime) model, assessing the costs and benefits of anticoagulation therapy. A published long-term model assessing the cost-effectiveness of directly acting oral anticoagulants compared with warfarin was identified and also assessed outcomes for antiplatelet treatment. It was deemed suitable for the long-term modelling of costs and benefits of cryptogenic stroke patients who have atrial fibrillation (whether detected or undetected). The following clinical outcomes were included in the model: ischaemic stroke, myocardial infarction, clinically relevant (extracranial) bleeding, intracranial haemorrhage, systemic embolism, transient ischaemic attack and death.

The studies identified in the systematic review informed the development of the two-stage de novo economic model. The first stage of the model was a short-term patient flow model to identify cryptogenic stroke patients with detected atrial fibrillation who are prescribed anticoagulation treatment and those who have undetected atrial fibrillation and remain on antiplatelet treatment. The second stage of the model used the long-term directly acting oral anticoagulant model, which captured the lifetime costs and benefits of patients on either anticoagulation or antiplatelet treatment.

The de novo economic model produced incremental cost-effectiveness ratios comparing implantable cardiac monitors with standard of care monitoring to detect atrial fibrillation in cryptogenic stroke patients. The monitors assessed were Reveal LINQ, BioMonitor 2-AF and Confirm Rx. The results of the pairwise analysis, that is each implantable cardiac monitor device compared with standard of care monitoring, demonstrate that implantable cardiac monitors are cost-effective at a standard £20,000–30,000 willingness-to-pay threshold, compared with standard of care monitoring. When each device was compared incrementally, BioMonitor 2-AF dominated Reveal LINQ and Confirm Rx. However, the results for BioMonitor 2-AF and Confirm Rx should be viewed with caution, as no data were available for any version of these devices in the cryptogenic stroke population; therefore, there is substantial uncertainty in the results.

Discussion

Clinical discussion

There is extremely limited diagnostic test accuracy or comparative clinical effectiveness evidence for the use of implantable cardiac monitors in the detection of atrial fibrillation, particularly in the cryptogenic stroke population. There is also evidence to suggest that atrial fibrillation detection in implantable cardiac monitor devices is dependent on various factors, including the patient population and incidence rate of atrial fibrillation, thus limiting the use of data in non-cryptogenic stroke populations to draw meaningful conclusions. The CRYSTAL-AF trial provides the most robust evidence on which to base conclusions of implantable cardiac monitor efficacy, although its open-label design introduces potential bias; for example, the outcome assessor was aware of the intervention assignment and was able to influence the assessment of atrial fibrillation. However, the atrial fibrillation detection rate from the CRYSTAL-AF trial is potentially a conservative estimate for the Reveal LINQ, as the mixed population diagnostic test accuracy studies suggest that the Reveal LINQ has fewer false positives and fewer false negatives than the Reveal XT; therefore, it is likely to be as effective, if not better, at detecting atrial fibrillation than the Reveal XT.

No studies were identified for the BioMonitor 2-AF or Confirm Rx devices in cryptogenic stroke populations, so evidence for these devices is limited to mixed population diagnostic test accuracy and single-arm observational studies submitted by the companies. No evidence was found for any device for several outcomes (mortality, hospital and outpatient care for atrial fibrillation, related morbidities, adverse events related to anticoagulation) and information about clinician ease of use and implantable cardiac monitor acceptability to patients was limited. Nevertheless, the evidence suggests that the newer models of the implantable cardiac monitors (e.g. Reveal LINQ and Confirm Rx) are easier to insert, associated with fewer adverse events and suitable for insertion by trained nurses and cardiac physiologists. There is also evidence that the implantable cardiac monitors detected some non-atrial fibrillation cardiac arrhythmias, although the potential benefit of this is unclear.

Cost-effectiveness discussion

The results of the pairwise analysis demonstrate that implantable cardiac monitors could be considered cost-effective at a £20,000–30,000 willingness-to-pay threshold, compared with standard of care monitoring. These results are comparable with the economic analysis produced by Diamantopoulos *et al.* (Diamantopoulos A, Sawyer LM, Lip GY, Witte KK, Reynolds MR, Fauchier L, *et al.* Cost-effectiveness of

an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. *Int J Stroke* 2016;**11**:302–12), which also used data from the CRYSTAL-AF trial to compare implantable cardiac monitors with standard of care monitoring.

Furthermore, expert clinical opinion suggests that an additional benefit of implantable cardiac monitor devices is the ability to detect non-atrial fibrillation arrhythmias, potentially preventing other events. However, data on incidental findings from implantable cardiac monitors were found only in observational studies and are of poor quality. As a result, it is unclear how detection of other non-atrial fibrillation arrhythmias differs between standard of care monitoring and implantable cardiac monitors and, furthermore, how a patient's treatment pathway changes. Therefore, understanding the differences in costs and benefits for incidental findings for implantable cardiac monitors is problematic. However, if some of these arrhythmias remain undetected without an implantable cardiac monitor, then the impact on the cost-effectiveness estimates would be favourable towards implantable cardiac monitors, but the size of the impact is difficult to determine.

Conclusions

The limited evidence suggests that the Reveal LINQ is more effective at detecting atrial fibrillation than conventional follow-up and is associated with low adverse event rates. However, there is insufficient clinical data available for the Confirm Rx and BioMonitor 2-AF in a cryptogenic stroke population, and so it is not possible to draw conclusions on their clinical efficacy or on how any of the implantable cardiac monitors might compare with each other.

Based on a strong assumption of clinical equivalency between all the devices, the economic analysis found that implantable cardiac monitors could be considered cost-effective at a £20,000–30,000 willingness-to-pay threshold, compared with standard of care monitoring. When each device was compared incrementally, BioMonitor 2-AF dominated Reveal LINQ and Confirm Rx.

Study registration

This study is registered as PROSPERO CRD42018109216.

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This report

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