Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: **Loop Recorders to Detect Atrial Arrhythmias in Patients Post-discharge who have had a Cryptogenic Stroke: A Review of Clinical and Cost-effectiveness**

DATE: 25 March 2014

CONTEXT AND POLICY ISSUES

Atrial fibrillation (AF) is a common cause of ischemic stroke and AF-associated strokes have higher morbidity and mortality than those from most other causes.[1] However, AF is often asymptomatic and intermittent ('silent paroxysmal AF'), both upon stroke presentation and with post-stroke monitoring.[1,2] Risk factors for silent paroxysmal AF have been listed as hypertension, age, elevated body mass index, diabetes mellitus, cigarette smoking, and previous cardiac disease.[3]

Optimal AF screening methods are essential post-stroke but current guidance as to how to effectively accomplish this is limited.[1,4] This is particularly true for the 20 to 30% of patients in whom no stroke etiology can be determined ('cryptogenic' strokes).[3] Once AF is identified, treatment with anticoagulant drugs reduces the annual risk of recurrent stroke by 40 to 60%,[1,5] although an additional challenge is that only 25 to 50% of patients with AF and thromboembolic risk factors are offered anticoagulant therapy and, within this group, long-term compliance is an issue.[3]

Although standard electrocardiograms (ECGs) are readily available, affordable and readily available, they capture less than a minute of cardiac rhythm so are minimally helpful for diagnosis of infrequent events.[1] Monitoring for post-stroke atrial arrhythmias generally involves 24-hour Holter monitoring (HM) via an externally worn device while a patient is still in hospital and sometimes extends to several days after discharge.[1] However, the equipment is intrusive and the detection rate of AF is low, (approximately 6%).[1] The longer monitoring is carried out, the higher the AF detection rate, leading to interest in modalities that allow monitoring for days, weeks, or even months after a cryptogenic stroke.[1,6]

Monitoring for several weeks is accomplished via external monitoring devices. The technology initially consisted of HMs with three to five electrodes attached to the patient, but there are at least two newer alternatives: (a) loop recorders with ECG electrodes attached to the patient that continuously collect new ECG information for up to six weeks;[1] and (b) leadless mobile outpatient cardiac telemetry (MOCT) systems that involve patient-activated event recorders. Both types of recorders have limited memory and can store only a few tracings, thus data are downloaded continuously or frequently via telephone or bluetooth technologies.[7]

Monitoring for weeks to months is accomplished via an implantable loop recorder (ILR), a leadless device the size of a small USB stick that records ECGs. The ILR is surgically inserted under the skin of the chest wall to overcome patient compliance issues and to allow a lengthier monitoring period (up to three years).[1,8] The device can detect arrhythmias automatically or may be triggered by the patient by placing an activator over it. Data are downloaded and reviewed remotely. ILR limitations include device cost and the need for surgical implantation.[1] An example ILR is the Reveal XT™ (Medtronic Inc., Minneapolis) that has a reported sensitivity of 96% and specificity of 85% for the detection of AF.[9,10]

The purpose of this report is to examine the clinical effectiveness, safety and cost-effectiveness of loop recorders (external and implantable types) for the detection of AF in patients who have suffered a stroke of unknown origin (a 'cryptogenic stroke').

RESEARCH QUESTIONS

1. What is the clinical effectiveness of loop recorders (external and implantable) to detect atrial arrhythmias, compared with Holter monitoring, for patients post-discharge who have had a cryptogenic stroke?
2. What is the evidence for the safety of loop recorders to detect atrial arrhythmias, compared with Holter monitoring, for patients post-discharge who have had a cryptogenic stroke?
3. What is the cost-effectiveness of loop recorders to detect atrial arrhythmias, compared with Holter monitoring, for patients post-discharge who have had a cryptogenic stroke?

KEY FINDINGS

The clinical evidence base identified for loop recorders includes four comparative studies (novel technology versus usual care) and, with the exception of one feasibility study, the novel technology showed superior rates of AF detection. A single economic analysis found monitoring to be cost-effective due to detection of AF and subsequent use of anticoagulant therapy. A number of larger studies are underway with two involving Canadian sites.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, and Canadian and major international health technology agencies as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and February 25, 2014.

Selection Criteria and Methods

Publications were selected if they were studies on adults monitored for atrial arrhythmias after being discharged from hospital after admission for a cryogenic stroke, according to the selection criteria outlined in Table 1. One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection.

Table 1: Study Selection Criteria

Population	Adult patients post-stroke (or TIA in some cases) who were monitored for AF as discharged OPs
Index Tests	Loop cardiac monitors – both external and implantable. (MCOT was also included as it is a similar technology.)
Comparator	Usual post-discharge care (generally short-term HM)
Outcomes	Q1: Clinical effectiveness: device sensitivity and specificity for detection of atrial fibrillation (or other atrial arrhythmias) compared with usual care; decisions for anticoagulation administration determined by device results Q2: Adverse events Q3: Cost-effectiveness compared with alternatives
Study Designs	Q1 & 2: HTAs / SRs / MAs; recent primary research if necessary, focussing on comparative studies Q3: Economic studies

AF=atrial fibrillation; HTA=health technology assessment; HM=Holter monitor; MA=meta-analysis; MCOT=mobile outpatient cardiac telemetry; OP=outpatient; SR=systematic review; TIA=transient ischemic attack

Exclusion Criteria

Studies were excluded from the review of clinical evidence if they did not compare results obtained using loop recorders versus usual care in patients post-cryptogenic-stroke (or transient ischemic attack [TIA] in some cases). Studies were also excluded if they reported monitoring that only occurred while patients were hospitalized post-stroke. In addition, there were two relevant studies not yet published in peer reviewed journals so they were not included among the reported studies. However, the information on these studies is shown in Appendix 1.

Critical Appraisal of Individual Studies

For the four included clinical studies, attention was paid to study size and design, blinding, representativeness of the patient population possible sources of bias such as funding and potential conflicts-of-interest, and any other study features that could impact study rigour. For the review of the single economic analysis, the 35-point Drummond Checklist was employed.[11]

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 369 references. After screening titles and abstracts, 343 potentially relevant references were excluded and 26 were selected for full-text review. Ten potentially relevant references were identified from other sources (grey literature, hand-searching, etc.). Of these 36 reports, 31 did not meet the study inclusion criteria and were excluded, leaving a total of four relevant references for the clinical review (including safety) and one for the economic review. On-going and / or unpublished clinical trials of relevance to this topic are provided in Appendix 1. The study selection process is outlined in the PRISMA flowchart in Appendix 2. The evidence for each research question is reported separately.

Summary of Study Characteristics

What is the clinical effectiveness of loop recorders (external and implantable) to detect atrial arrhythmias, compared with Holter monitoring, for patients post-discharge who have had a stroke of unknown origin ('cryptogenic stroke')?

Four studies met the inclusion criteria (Table 2; details in Appendices 3 to 5). All were recent (2013) and prospective, comparing interventions in adult patients who had been admitted for a cryptogenic stroke (and high risk TIA in some cases). The interventions included some form of longer-term outpatient cardiac rhythm monitoring versus usual post-discharge monitoring (this varied within and across studies and was often poorly described). The primary goal of all studies was to measure the detection rate of AF and some commented on subsequent anticoagulant management that resulted. In three studies, the intervention involved an external monitoring device,[4,12,13] and in one study the intervention was a small monitoring device implanted under the skin.[8] The studies were performed in France, Germany, Scotland and the USA. Industry funding or involvement were not evident aside from one study where devices and training were supplied by a manufacturer.[13]

Table 2: Overview of Included Clinical Studies

First Author, Year, Country	Sample Size (n)	Index test	Comparator	Primary Clinical Outcome
External cardiac monitors				
Higgins,[13] 2013, Scotland	n=100	CEM	Usual care	AF detection rate
Kamel,[12] 2013, USA	n=40	MCOT	Usual care	AF detection rate
Suissa,[4] 2013, France	n=946	CEM	Usual care	AF detection rate
Implanted cardiac monitors				
Ritter,[8] 2013, Germany	n=60	ICM	7-day Holter after ICM implanted	AF detection rate

KEY: AF=intermittent atrial fibrillation; CEM=continuous electrocardiographic monitoring; ICM=implanted cardiac monitor; MCOT=mobile cardiac outpatient telemetry

What is the cost-effectiveness of loop recorders to detect atrial arrhythmias, compared with Holter monitoring, for patients post-discharge who have had a cryptogenic stroke?

One relevant economic analysis was identified, a USA analysis by Kamel et al.[14] Using a Markov model and assuming a health care payer perspective, the authors performed a cost-utility analysis of outpatient cardiac monitoring after ischemic stroke in a hypothetical cohort of 70-year-old patients. Their aim was to determine the lifetime cost and utility of warfarin therapy in those diagnosed with AF. Two strategies were modelled: (1) standard care with no outpatient cardiac monitoring plus aspirin prescribed, versus (2) one week of outpatient cardiac monitoring which could detect AF and trigger a change from aspirin to warfarin. The week of outpatient monitoring involved an event-triggered loop recorder (assumed to be external, though not specified) at an estimated cost of $168 per patient including equipment, technician services, and physician interpretation. Detail is contained in Appendices 6 and 7.

Summary of Critical Appraisal

All clinical studies were prospective and comparative. Two of the studies were described as pilots and types of devices employed were unique to each study. Three of the studies were small (≤ 100 patients) and none involved blinding of patients or investigators (a technically difficult exercise). Two of four were randomized.[12,13] With respect to selection of patients and generalizability, three studies enrolled all patients with cryptogenic stroke treated at stroke units;[4,12,13] however, in the fourth study that employed ICM, of 233 patients with cryptogenic stroke 95 (41%) were considered to be ICM candidates and only 60 agreed to the treatment (26% of the total, 63% of those considered eligible).[8] Onset of monitoring post-stroke was variable, ranging from immediately[4] to a mean of 22 days post-stroke.[12] Two studies commented on changes in management and shorter-term outcomes[8,13] but two did not.[4,12] Long-term outcomes were not evaluated in any studies. No studies reported industry funding although one did not reveal study funding or conflict-of-interest[4] and one employed equipment and training supplied by the device manufacturer.[13]

In the economic analysis,[14] the authors started with a clinical step, i.e., they estimated the AF detection rate for outpatient monitoring by performing a systematic review. Rigorous steps were clearly described in the publication, i.e., a broad literature search was undertaken and the literature was reviewed and data extracted by two authors with disagreements resolved by a third; degree of heterogeneity was measured; and a meta-analysis was performed. Review of the economic analysis was guided by the Drummond Checklist and the analysis performed well, satisfying essentially all of Drummond's specified items.[11] For example, the research question, sources of effectiveness estimates, and choice of time horizon and discount rates are clearly stated. An approach to sensitivity analysis is given and conclusions follow from the data reported.

Summary of Findings

What is the clinical effectiveness of loop recorders (external and implantable) to detect atrial arrhythmias, compared with Holter monitoring, for patients post-discharge who have had a stroke of unknown origin ('cryptogenic stroke')?

One study reported no detection of AF in either group although the study was small (n=40) and focused on feasibility.[12] Despite the variation in the designs of the other three studies (technology, length of monitoring, sample size, etc.) all three detected statistically significantly higher rates of AF post-stroke in the intervention group versus the usual care group, i.e., 44% versus 4% ($P < 0.001$) in the Scottish study using an external device,[13] an adjusted odds ratio of 5.29 (95% Confidence Interval [CI] 2.43 to 11.55) in the French study also using an external device,[4] and 17% (95% CI 7% to 26%) versus 1.7% (95% CI 0% to 5%) in the German study using an implantable device (P = 0.0077).[8]

The goal of seeking silent AF in patients post-cryptogenic stroke is to offer anticoagulant therapy in the hope of preventing recurrent strokes because the evidence has shown a significant clinical benefit.[1] Two studies assessed the impact of their findings on changes in management. In a Scottish study of 100 patients,[13] the higher AF detection rate in the intervention group (44% versus 4% for any AF and 18% versus 2% for sustained AF) led to use of anticoagulants in 16% of patients versus zero controls. At 90-day follow-up there was no difference between groups for clinical stroke, TIA, myocardial infarction or death. In the German study of 60 patients,[8] AF was detected in 10 versus 1 patient and all patients diagnosed with AF were offered anticoagulant therapy (although actual drug uptake was not reported). Subsequent clinical outcomes were not reported.

What is the evidence for the safety of loop recorders to detect atrial arrhythmias, compared with Holter monitoring, for patients post-discharge who have had a cryptogenic stroke?

All four studies monitored adverse events as a safety outcome but no adverse events were detected aside from a single report of contact dermatitis from the external device in one study[13] and a comment that women sometimes found the external device uncomfortable when wearing a bra in another (the number of times this complaint was made was not reported).[8] The product

brochure for the Reveal XT implantable device provides detailed safety information including the fact that patients should avoid sources of diathermy (e.g., used in physical and occupational therapy to deliver moderate heat); high sources of radiation, electrosurgical cautery, external defibrillation, lithotripsy, therapeutic ultrasound and radiofrequency ablation. The brochure further stated that magnetic resonance imaging (MRI) scans should be performed only in a specified environment. Potential complications were reported to include, but were not limited to, device rejection phenomena (including local tissue reaction), device migration, infection, and erosion through the skin.[9] No details on the rates of these events were provided.

What is the cost-effectiveness of loop recorders to detect atrial arrhythmias, compared with Holter monitoring, for patients post-discharge who have had a cryptogenic stroke?

The authors performed a cost-utility analysis of outpatient cardiac monitoring after ischemic stroke.[14] Perspective was that of a health maintenance organization or insurance company paying for medical care and prescription drugs. Productivity was deemed to be a minor consideration due to patient age. Costs and life-years were discounted at 3% and costs and utilities were projected over a maximum of 20 years (median expected survival was 13.3 years). Costs were converted to 2010 dollars and cost-effectiveness was determined to be a cost-utility ratio (CUR) of < $50 000 per QALY.

The clinical meta-analysis, conducted on the post-stroke incidence of AF detected by outpatient monitoring, returned a diagnosis rate of 6% versus 1.5% for patients without additional monitoring (i.e., a 4.5% difference). The modelling estimated that, for a hypothetical 70-year-old patient post-stroke in whom AF was detected, lifelong warfarin therapy would result in a gain of about 0.8 quality-adjusted life-years (QALYs) and would cost $1627 more than aspirin. Outpatient cardiac monitoring would detect 59 new cases of AF for every 1000 patients monitored compared with 15 new cases without monitoring (i.e., a difference of 44 patients per 1000). By triggering warfarin therapy, this would result in a comparative gain of 34 QALYs. The cost-utility ratio of outpatient cardiac monitoring was calculated at US $13,000 per QALY.

For the sensitivity analysis, the CUR of outpatient monitoring was plotted for a range of values of key model inputs and the information displayed in bar graph format in the publication. Outpatient monitoring remained cost-effective throughout a wide range of model inputs in sensitivity analyses, including changes in the cost and yield of monitoring. In particular, monitoring was cost-effective at any AF detection rate > 0.8% and any cost < $2000 per patient. The authors concluded that a week of outpatient cardiac monitoring after stroke is cost-effective (versus no outpatient monitoring) though they noted that the optimal length of monitoring was unknown.

A follow-up letter by other experts[15] noted that the economic benefit of extended outpatient monitoring for AF post-stroke may be even more attractive for several reasons: (1) in a study of their own the AF detection rate was 12.5% (twice that calculated by the authors of the economic analysis); and (2) additional medications (beta blockers) included in the original analysis are likely not required. These changes dropped the cost per QALY to about US $5,100.

Similarly, one of the included clinical studies [13] elaborated on the economic analysis described above. The Scottish authors noted that the cost-effectiveness of longer-term monitoring would be even more favourable employing their findings (16% difference between groups) versus that estimated by Kamel et al. where the AF detection rate difference was 4.5%.

LIMITATIONS

A significant limitation is the fact that the main outcomes of available studies relate to detection rate of AF without consistent long-term tracking of changes in patient management or clinical outcomes. The latter two considerations may be forthcoming because longer planned study follow-up is anticipated.[8] The number of available studies is still small although there are at least five additional studies underway or recently completed (Appendix 1) and peer-reviewed study results from these studies may soon be available. In particular, two of these studies are large and both involve Canadian centers (EMBRACE [external monitors] and CRYSTAL-AF [implantable monitors]). The evidence base is challenging as there are few studies comparing the newer technologies with usual care and no studies comparing newer technologies to each other. In addition, the studies vary widely in a number of ways, for example, the point post-stroke at which patients are enrolled, inclusion of patients with TIA and stroke or stroke only, definition of cryptogenic stroke, definitions and consistency of usual care, duration of monitoring, definition of clinically significant AF, type of technology employed, and continuous versus intermittent data capture. It is unclear how well the single economic analysis, performed in California in 2010 dollars, would extrapolate to the Canadian health care setting in 2014.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In up to 30% of patients who experience an ischemic stroke, no underlying cause can be found on admission or during hospitalization.[3,8] There is growing interest in monitoring these patients to detect underlying AF for days, weeks or even months post-discharge with a goal to detecting the silent AF that may be a major contributor. The benefit to AF detection is the opportunity to offer anticoagulant drug treatment, as it has been shown to prevent a number of future strokes.[1] Several types of long-term monitoring devices have been reported including implanted and external loop recorders and external MOCT. The latter are employed for days to weeks whereas the former is employed for up to three years.

Four studies were identified that compared one of these technologies to usual care (i.e., limited or no post-discharge monitoring). No studies compared one technology to another. A small feasibility study (n=40)[12] found no difference between groups but the other three reported significant differences in the technology's ability to detect episodes of AF. A single economic analysis found post-discharge monitoring to be cost-effective due to detection of AF and subsequent use of anticoagulant therapy. Two other groups of authors supported this observation and noted that it may even be an under-estimate of economic benefit, depending on rate of AF detection and use of other medications. A number of larger studies are underway with two involving Canadian sites.

In addition to the comparative studies, a number of non-comparative cohort studies followed patients post-cryptogenic stroke to determine AF detection rates (Table 3).

Table 3: Non-comparative Cohort Studies

First author, year, country	n=	Device	AF detection rate	Other
Cotter,[16] 2013, England	51	Reveal XT™	26% (median monitoring duration before AF = 48 days [range 0-154 days])	Median AF duration was 6 minutes
Etgen,[17] 2013, Germany	22	Reveal XT™	27% by 1 year (median monitoring duration before AF = 5 months); AF was silent in 67% of patients	AF was silent in 67% of patients
Flint,[18] 2012, USA	239	CardioPAL SAVI™	12% in 28 days of monitoring (range 18-30); AF was silent in 94% of patients	Data from a 3-year, prospective multicenter registry
Miller,[5] 2013, USA	156	CardioNet®	Mean of 17% (increased with monitoring time from 4% at 2 days to 9% at 7 days, 15% at 14 days, and 20% at 21 days)	

KEY: AF=intermittent atrial fibrillation

Despite optimistic research findings, there are several issues for decision-makers. The evidence base is sparse without adequate tracking of the impact of AF detection on changes in patient management and outcomes. It is unclear which patients are the best candidates for post-stroke monitoring and how the benefits of the various technologies compare to each other. The available studies vary in patient groups studied (e.g., stroke versus TIA, definition of cryptogenic, etc.; type of technology used; onset, length and frequency of monitoring; and definition of clinically significant AF). In addition, little cost-effectiveness information is available.

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APPENDIX 1: List of On-going or Unpublished Clinical Trials

A. EXTERNAL CARDIAC RECORDERS

1. *Detection of Occult Paroxysmal Atrial Fibrillation after Stroke Using Prolonged Ambulatory Cardiac Monitoring* (Mayo Clinic, Rochester, MN)

   ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29-. Identifier NCT01325545. Detection of occult paroxysmal atrial fibrillation after stroke using prolonged ambulatory cardiac monitoring; 2012 Dec 21 [cited 2014 Feb 28]. Available from: clinicaltrials.gov/ct2/show/NCT01325545?term=cryptogenic+stroke+atrial+fibrillation&rank=3

   The main goal of the prospective, observational, randomized, case-control study was to determine the prevalence of occult paroxysmal AF in 132 patients with cryptogenic stroke or TIA. The intervention group was assigned three weeks of CardioNet Mobile Cardiac Outpatient Telemetry (MCOT™) versus a control group. The study started in April 2009 and data collection ended in March 2011; however, no reports of outcomes are available. The study funder is not described but CardioNet is listed as a study collaborator.

2. *30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE)* (Canada: 16 centres in four provinces)

   ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29-. Identifier NCT00846924. 30-Day cardiac event monitor belt for recording atrial fibrillation after a cerebral ischemic event (EMBRACE); 2014 Jan 20 [cited 2014 Mar 2]. Available from: clinicaltrials.gov/ct2/show/NCT00846924?term=EMBRACE&rank=4

   The purpose of this prospective, randomized study was to determine the AF diagnostic yield of 30-day cardiac monitoring using the AccuHeart Electrode Belt (Cardiac Bio-Systems) and Braemar event-triggered loop recorder, compared to a control group that received 24-hour Holter monitoring. Patients (n=572) were required to be age 55+ (mean age 73 years) with a cryptogenic stroke or TIA in the previous six months. The study started in May 2009 with final data collection planned for April 2014. No formal publications are available; however, preliminary results showed a rate of AF (> 30 seconds) of 16% in the monitored group versus 3% in the control group ($P < 0.001$).[19] If AF was detected, 72% of patients received anticoagulation. Treatment increased in the 30-day monitoring group from 5% to 18% by 90 days compared with 10% in controls. Overall, the number-needed-to-screen (NNS) was calculated as eight and diagnostic yield was highest in patients aged 75+ where NNS was six. Compliance was high, with 85% of patients completing at least three weeks of CEM.[20] Two-year-follow-up is underway. There is no industry funding noted for this study.

B. IMPLANTABLE CARDIAC RECORDERS

1. *CRYSTAL-AF (**CRY**ptogenic **ST**roke **A**nd under**L**ying **AF**) Trial (International)*:

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29-. Identifier NCT00924638. Study of continuous cardiac monitoring to assess atrial fibrillation after cryptogenic stroke (CRYSTAL-AF); 2014 Jan 9 [cited 2014 Mar 2]. Available from: clinicaltrials.gov/ct2/show/NCT00924638?term=crystal+cardiac&rank=1

The purpose of the randomized, open label, parallel group assignment study was to evaluate the time to first AF in subjects with a recent cryptogenic stroke or TIA. Sponsored by Medtronic Cardiac Rhythm Disease Management, the Phase IV study commenced in 2009 and enrolled 448 patients at 57 centres in the US, Canada and 12 countries in Europe. The intervention group received continuous rhythm monitoring using a Reveal® XT Insertable Cardiac Monitor (device cost $4000) whereas the control group received a variety of forms of conventional post-stroke monitoring. Although the study has ended, no formal publications are yet available; however, some outcomes data are available:[21] at 6, 12 and 36 months, AF detection rates for intervention group patients were about 9%, 12% and 30% versus controls at 1%, 2% and 3%, respectively (all results were significant). The median time to find AF in the intervention group was 84 days. Among patients found to have AF, oral anticoagulants were prescribed for 97% of cases. There were reportedly fewer strokes in the intervention arm, but the data were not provided and the authors noted that the study was not powered to show a reduction in stroke. Devices were removed in 2.4% of patients and no long-term problems were reported.

2. SCARF *(Extended Rhythm **SC**reening for **A**t**R**ial **F**ibrillation in Cryptogenic Stroke Patients)* (Netherlands):

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29-. Identifier NCT01550042. Extended rhythm screening for atrial fibrillation in cryptogenic stroke patients (SCARF); 2012 April 20 [cited 2014 Feb 28]. Available from: clinicaltrials.gov/ct2/show/NCT01550042?term=cryptogenic+stroke+atrial+fibrillation&rank=2

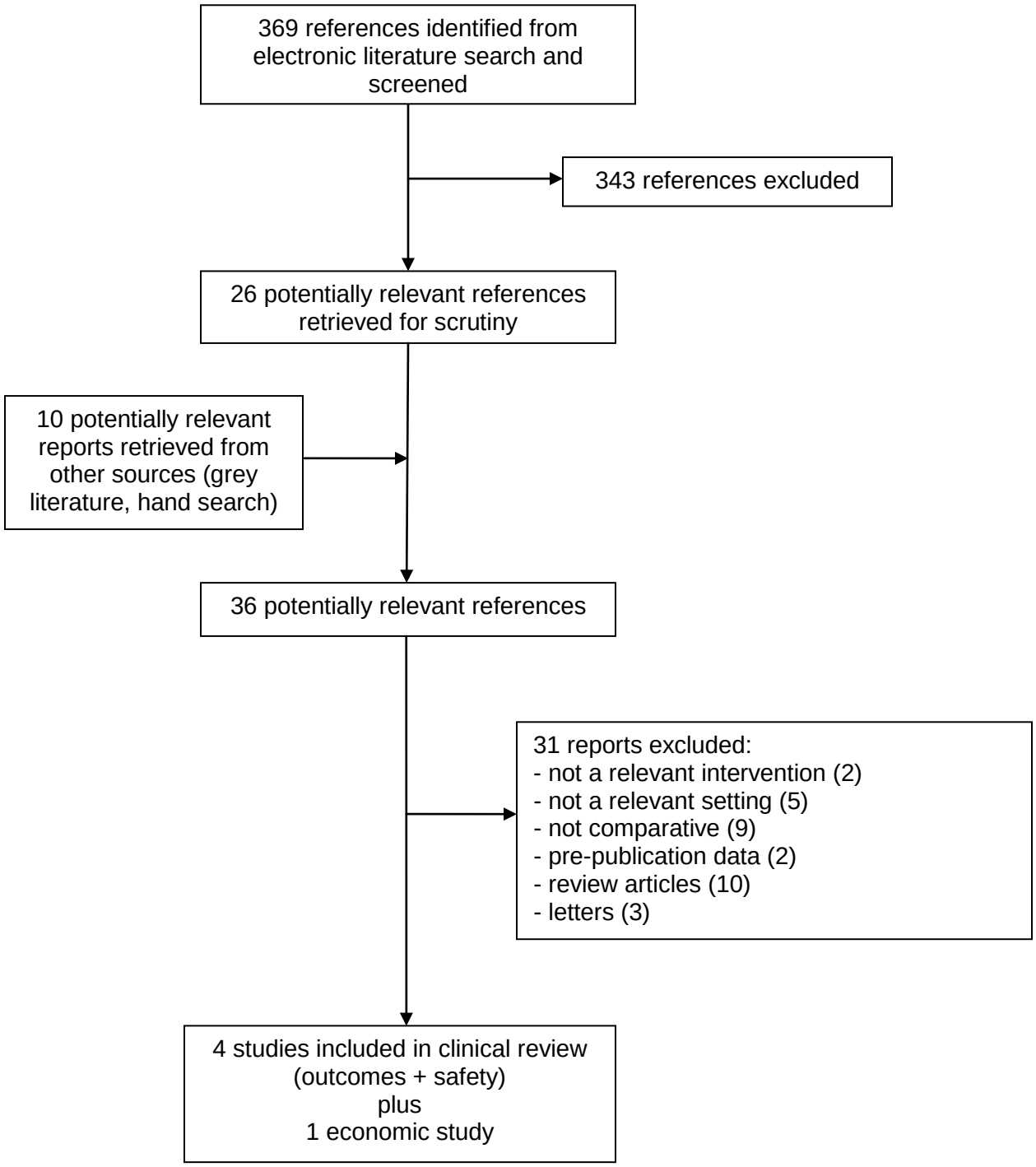
The prospective observational study measured how many of 50 enrolled patients post-cryptogenic-stroke (within 60 days) had documented AF based on 12 months of data from implantable cardiac monitors. The study started in September 2009 and data collection ended in September 2011 but no publications were identified.

3. *SURPRISE Trial (Copenhagen, Denmark)*:

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29-. Identifier NCT00310180. Finding atrial fibrillation in patients with unexplained stroke using long-term cardiac monitoring (SURPRISE); 2012 Sept 13 [cited 2014 Feb 28]. Available from: clinicaltrials.gov/ct2/show/NCT01498146?term=cryptogenic+stroke+atrial+fibrillation&rank=8

The study purpose is to monitor for AF in patients with a cryptogenic stroke or TIA using up to three years of data from an implanted cardiac monitor. The study has recruited 100 patients at a single Copenhagen hospital and data collection was to cease in October 2013. No study funder was mentioned.

APPENDIX 2: Selection of Included Studies



APPENDIX 3: Summary of Characteristics of Included Clinical Studies

Table A1: Summary of Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size (n)	Index test	Comparator	Clinical Outcomes
External cardiac monitors					
Higgins,[13] 2013, Scotland (2 centres in Glasgow)	Prospective, randomized, comparative	Adults admitted for stroke or TIA (mean age 66; 44% women; 68% stroke); n=100	CEM (Novacor R-test Evolution-3 device) within 7 days of stroke onset – device triggered by AA, recording each episode for 30 seconds	Usual care including ECG at 24 & 72 hours as per CPGs & national practice	AF detection rate at 14 and 90 days
Kamel,[12] 2013, USA	Prospective, randomized, comparative, Phase 1, focussed on feasibility, i.e., enrollment, completion of monitoring & follow-up	Adults admitted for cryptogenic stroke or high-risk TIA (mean age 67; 43% women); n=40	CardioNet MCOT monitor x 21 days	Usual care (no details were provided)	New diagnoses of AF at 3 months and 1 year
Suissa,[4] France	Prospective, comparative, non-randomized (patient was assigned to ICU or Stroke Unit by physician)	Consecutive adults with stroke without AF on baseline ECG (mean age 63; 46% women); n=946	Patients admitted to ICU (n=592; 63%) received the CEM (Infinity Central Station device [Lübeck, Germany]) upon admission	Patients admitted to Stroke Unit (n=354; 37%) had routine practice, i.e., 24-hour HM & additional ECGs as indicated while in hospital	AF detection rate
Implanted cardiac monitors					
Ritter,[8] 2013, Germany	Prospective, comparative (patients were their own controls)	Adults admitted for cryptogenic stroke (mean age 62; 43% women); n=60	ICM implanted under LA 13 days post-stroke (interquartile range 10-65 days); follow-up until AF dx or at least 12 months	7-day HM performed after ICM implanted & daily 7-minute ECG transmitted via telephone	AF detection rate (plus feasibility of ICM)

KEY: AA=atrial arrhythmia; AF=intermittent atrial fibrillation; CEM=continuous electrocardiographic monitoring; CPG=clinical practice guideline; dx=diagnosed / diagnosis; ECG=electrocardiogram; HM=Holter monitor; ICM=implanted cardiac monitor; LA=local anesthetic; MCOT=mobile cardiac outpatient telemetry; TIA=transient ischemic attack

APPENDIX 4: Summary of Critical Appraisal of Included Studies

Table A2: Summary of Critical Appraisal of Included Clinical Studies

First Author, Publication Year	Strengths	Limitations
External cardiac monitors		
Higgins,[13] 2013	• Prospective 'pilot' study • Randomization via an interactive voice response system • ECG data were interpreted by independent experts • Impact on management was presented	• Blinding was not attempted • Small sample size (designed as a pilot) • Sample skewed to milder strokes • Recording was fairly short-term (7 days) • Limited generalizability with only two centres involved • Device had limited memory and AF detection capacity (has now been upgraded [R-test Evolution 4]) • The device manufacturer contributed six devices plus training though was not otherwise involved in the study
Kamel,[12] 2013	• Prospective 'pilot' study • Randomization via random permuted blocks of varying sizes • All device-labelled AF episodes manually reviewed by cardiologist • No report of industry involvement or COI	• Blinding was not attempted • Small sample size (designed as a pilot) • Designed as a feasibility study; AF detection rate was a secondary outcome measure • Compliance with monitoring was only 64% (25% were totally non-compliant), possibly due to the inconvenience of multiple leads • Monitoring did not start until 22 days (± 12) post-stroke • Not possible to track impact on management or outcomes
Suissa,[4] 2013	• Prospective / consecutive patients • Large sample size	• Blinding was not possible • Single centre study • No randomization – intervention depended on hospital unit with decision made by admitting physician • Study groups not equal, i.e., those in ICU more severe • Included patients were diverse – only excluded from study if no AF on admission • Cardiac device could not capture specific arrhythmias but was set to detect pulse > 120 beats, i.e., there was no automatic detection software • No comment on subsequent treatment or clinical outcomes • NO COI or study funding information
Implanted cardiac monitors		
Ritter,[8] 2013	• Prospective & comparative • ECG transmissions reviewed by two independent cardiologists • Only episodes dx as AF by humans were deemed to be AF • Median follow-up > 1 year (382 days) • Noted changes in management & outcomes • No report of industry involvement or COI	• Blinding was not possible • Small sample size • Single centre study • Only 2/3 of eligible patients agreed to participate in the study (60 of 95) • Variation in time of implant post-stroke (mean of 13 days, interquartile range 10-65 days) • Compliance with 7-day HM was poor (mentioned but no details provided)

AF=atrial fibrillation; CIO=conflict-of-interest; dx=diagnosed; ECG=electrocardiogram

APPENDIX 5: Summary of Clinical Study Findings

Table A3: Summary of Study Findings and Authors' Conclusions for Included Clinical Studies

Author, Year	Main Study Findings	Authors' Conclusions
External cardiac monitors		
Higgins,[13] 2013	• At follow-up 14 days post-stroke, the intervention group showed significantly different detection rates of 44% for any AF and 18% for sustained (>20 seconds) AF versus 4% and 2% for the control group. Findings were sustained at 90-day follow-up. • Anticoagulants were employed in 16% of intervention group patients versus 0% of controls (p<0.05).	• Non-invasive monitoring after stroke increases detection of AF and impacts management using anticoagulants. • The authors recommended that eligible patients should be offered extended monitoring and CPGs should be modified to reflect this care.
Kamel,[12] 2013	No patient in either study arm was diagnosed with AF. Cardiac monitoring revealed brief episodes of atrial tachycardia in 2 patients (10%) and non-sustained ventricular tachycardia in 2 patients (10%).	This small feasibility study uncovered issues related to compliance related to external cardiac monitoring.
Suissa,[4] 2013	• After adjustment (demographic data, vascular risk factors, and stroke scale score), CEM increased by 5-fold the odds of finding AF (95% CI 2.4-11.6) compared to the routine strategy. • The adjusted OR was most favourable on the first day of monitoring (9.8) and then decreased. • CEM usefulness was not significantly higher than the routine strategy by 5 days.	The authors recommended that routine CEM should be employed in stroke units (minimum of 4 days).
Implanted cardiac monitors		
Ritter,[8] 2013	• AF detected in 10 patients (17%; 95% CI, 7-26%) via ICM versus 1 patient (2%) via 7-day HM • AF episodes were detected a mean of 64 days after implantation (range 1-556 days). • AF duration ranged from 2 minutes to >1500 hours • All patients dx with AF were advised to start on anticoagulants (compliance rate NR) • There were no strokes after 1 year of follow-up	ICM implantation was feasible in outpatients post-stroke and offered a higher diagnostic yield than 7-day HM.

AF=atrial fibrillation; CEM=continuous electrocardiographic monitoring; CI=confidence interval; dx=diagnosed; HM=Holter monitor; NR=not reported; OR=odds ratio

APPENDIX 6: Summary of Characteristics of Included Economic Study

Table A4: Summary of Characteristics of Included Economic Study

Author, Year, Country	Type of Evaluation, Perspective	Patient Population	Intervention	Comparator	Assumptions
Kamel,[14] 2010, USA	CUA (semi-Markov model), payer perspective	Hypothetical cohort of 70-year-old patients with AF, prior stroke, and no contraindication to warfarin therapy	Standard care after ischemic stroke with ASA prescribed plus 7 days of OP cardiac monitoring which could detect AF and trigger a change from aspirin to warfarin	Standard care after ischemic stroke with ASA prescribed and no OP cardiac monitoring	• Cost-effectiveness was defined as CUR < 50,000 per QALY. • Cost of one week of OP monitoring with an event-triggered loop recorder was $168. • Monitoring would incidentally reveal potentially serious cardiac arrhythmias other than AF in 5% of patients triggering a cardiology evaluation at a cost of $150. • Rate of recurrent stroke due to AF was 4.5% despite ASA. • Relative risk of stroke with warfarin versus ASA was 0.48. • Annual risk of hemorrhage due to warfarin was 0.4% • Relative risk of hemorrhage with ASA vs warfarin was 0.59. • AF detection would change treatment to warfarin in all cases (those with existing indications for or contraindications to warfarin would not undergo monitoring; all patients without AF would be treated with ASA). • Patients diagnosed with AF would get life-long generic beta blockers (annual cost $403).

KEY: AF=atrial fibrillation; ASA=acetylsalicylic acid; CUA=cost utility analysis; OP=outpatient

APPENDIX 7: Summary of Economic Analysis Findings

Table A5: Summary of Findings and Authors' Conclusions for Included Economic Analysis

Author, Year	Main Study Findings	Authors' Conclusions
Kamel,[14] 2010	• In a 70-year-old patient with non-valvular AF and prior ischemic stroke, lifelong warfarin therapy would result in a gain of about 0.8 QALYs and would cost $1627 more than ASA (includes the higher cost of warfarin therapy minus the cost savings from fewer strokes compared with ASA). • OP cardiac monitoring would detect 59 new cases of AF for every 1000 patients monitored compared with 15 new cases that would be diagnosed per 1000 patients without monitoring. • By triggering warfarin therapy, this would result in a comparative gain of 34 QALYs (12 for standard care vs 46 for OP monitoring). • The cost of monitoring 1000 patients would be $168,000; the cost of beta-blocker therapy and the comparative cost of warfarin in those identified to have AF would be $264,000, and the cost of cardiology consultation in those with an incidentally discovered arrhythmia other than AF would be $7500. This resulted in a net cost of approximately $440,000. • The CUR of OP cardiac monitoring would be approximately $13,000 per QALY gained.	*"Our analysis suggests that one week of outpatient cardiac monitoring after ischemic stroke is cost-effective." (P. 1519)* *"Our study may justify changing [clinical] guidelines so that routine outpatient cardiac monitoring is recommended." (P. 1519)* *"We recommend at least one week of outpatient cardiac monitoring to detect underlying AF in patients with unexplained stroke." (P. 1519)*
	Sensitivity analysis	
	• Monitoring was cost-effective at any AF detection rate > 0.8% and any monitoring cost < $2000 per patient. • OP monitoring remained cost-effective even if up to 85% of patients with underlying AF were to be diagnosed without OP monitoring and started on warfarin before a recurrent stroke. • OP monitoring after stroke remained cost-effective even if it were to lead to the maximum reasonable proportion of patients undergoing additional interventions such as electrophysiological study or pacemaker implant. • OP monitoring would only fail to be cost-effective if the patient was age > 82.	*"Outpatient cardiac monitoring is cost-effective after ischemic stroke over a wide range of model inputs" (P. 1514)*

KEY: AF=atrial fibrillation; ASA=acetylsalicylic acid; CUR=cost utility ratio; OP=outpatient; QALY=quality adjusted life year