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Title: Clinical and health economic evaluation of a post stroke arrhythmia monitoring service

Short Title: Post stroke arrhythmia monitoring

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Key Words: Atrial fibrillation, stroke, economic evaluation, recurrent stroke

Key Message: Developing a post-stroke arrhythmia monitoring service using R-TEST devices is feasible, effective at detecting AF and represents a probable net clinical and health economic benefit.

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Learning points

Routine post stroke arrhythmia monitoring using R-TEST is feasible, effective at detecting AF, and represents a probable clinical and economic benefit.

Staff education is key to ensuring appropriate patients are referred.

Abstract

Background: Atrial fibrillation (AF) is a major cause of recurrent stroke and transient ischaemic attack (TIA) in the UK. As many patients can have asymptomatic paroxysmal AF, prolonged arrhythmia monitoring is advised in selected patients following a stroke or TIA. This service evaluation assessed the clinical and potential health economic impact of prolonged arrhythmia monitoring post stroke using R-TEST monitoring devices.

Methods: This was a prospective case controlled service evaluation in a single health board in the North of Scotland. Patients were included if they had a recent stroke or TIA, were in sinus rhythm, and did not have another indication for, or contraindication to, oral anticoagulation. A health economic model was developed to estimate the clinical and economic value delivered by the R-TEST monitoring. Approval to use anonymised patient data in this service evaluation was obtained.

Results: During the evaluation period, 100 consecutive patients were included. The average age was 70 ± 11 years, 46% were female. Stroke was the presenting complaint in 83% patients with the other 17% having had a TIA. AF was detected in 7 of 83 (8.4%) patients who had had a stroke and 1 of 17 (5.9%) patients with a TIA. Health economic modelling predicted that adoption of R-TEST monitoring has a high probability of demonstrating both clinical and economic benefits.

Conclusions: Developing a post stroke arrhythmia monitoring service using R-TEST devices is feasible, effective at detecting AF, and represents a probable clinical and economic benefit.

Introduction

Cerebrovascular disease is a **major** cause of disability and mortality in adults worldwide (1). Patients can present with a stroke or transient ischaemic attack (TIA). Due to the risk of recurrent events, early investigation and treatment of risk factors is advised (2,3). One of the major risk factors for stroke is atrial fibrillation (AF). AF is a common cardiac arrhythmia which is estimated to affect 2.5% of the adult population in Scotland, with a large proportion undiagnosed and consequently untreated. Cardioembolism accounts for around a quarter of all ischaemic strokes, which is most commonly caused by AF (4). Current evidence shows that, in up to 24% of all patients presenting with AF induced ischemic stroke or TIA, the event is the first clinical documentation of AF (5,6). The clinical demand is significant because AF-related strokes are also associated with greater stroke severity and a poorer prognosis (7,8). Without adequate treatment of AF with oral anticoagulants, the annual risk of stroke recurrence in these patients also remains high (~20%) (9,10). However, the risk of stroke in AF patients following appropriate anticoagulation with warfarin is reduced by 45-69% (9,11) and additional benefits may be achieved with direct oral anticoagulants (12).

While many patients will have permanent or persistent AF, others will have intermittent paroxysmal AF (pAF; AF interspersed with periods of normal sinus rhythm), which can make diagnosis difficult, especially if the periods of AF are asymptomatic. In patients with pAF the risk of stroke is similar to permanent AF (13) and most guidelines do not differentiate between AF and pAF with regard to anticoagulation. Nevertheless, this is an area of research interest, on account of the increasing awareness that the total burden of AF correlates with stroke risk (14).

It is estimated that asymptomatic pAF is present in up to 16% of patients who have had a stroke, although rates vary depending on the mechanism and duration of monitoring (15,16).

This has led to a change in national guidelines which now advise post-stroke arrhythmia monitoring for at least 24 h in cases where cause of stroke is not obvious and where anticoagulation may be considered (2), although longer periods may be beneficial to increase detection rates (6). Due to the risk of early recurrent stroke and the evidence supporting timely anticoagulation (3), monitoring should be undertaken without undue delay. However, the duration of monitoring and implementation of these guidelines remains inconsistent and is debated for a variety of historical and logistical reasons (17).

In our centre, an arrhythmia monitoring service has been established for stroke and TIA patients in sinus rhythm at the time of presentation, not known to have AF or pAF, or any other indication for anticoagulation and with no absolute contraindications to anticoagulation. Patients are monitored for ~7-days with an R-TEST device to identify patients with AF/pAF and to allow subsequent intervention with anticoagulation.

The aim of this project was to evaluate this post-stroke arrhythmia monitoring service in terms of clinical effectiveness (identification of patients with AF and appropriate anticoagulation) and potential health economic benefit.

Methods

Design and Setting

This was a prospective case control service evaluation in patients who had a newly diagnosed stroke or TIA. Evaluation took place in Raigmore Hospital, the principal hospital of the NHS Highland Health Board, serving a predominantly remote and rural population in the North of Scotland. The health board is geographically the largest in Scotland covering 32,500km² and providing care for ~320,000 people.

Participants

Inpatients and outpatients diagnosed with non-haemorrhagic stroke or TIA between 20th June 2019 and 3rd July 2020 were considered for this study. Patients were included if they were in sinus rhythm at the time of presentation, not known to have AF (or pAF) or another indication for anticoagulation and with no absolute contraindications to anticoagulation (Figure 1). All eligible referrals from the stroke unit were accepted for monitoring.

Protocol

Patients were identified by a member of the stroke team and referred for an R-TEST monitor (Figure 2) (R-TEST 4, Novacor UK Ltd) either as an inpatient or outpatient. Seven devices were purchased for this study and subsequent clinical use. The monitors were fitted by a member of the cardiac physiology team using a standard technique. The R-TEST was configured to a dedicated AF/pAF algorithm (which relies on RR analysis combining wavelet transform and fractal analysis) with ECG strips being recorded from 60 s pre- until 40 s post-AF detection (total ECG strip length of 100 s). A maximum of 14 strips could be recorded for AF events (during the recording period). The device was able to report the presence of AF,

AF burden (%), longest episode of AF and the time from fitting the monitor to detection of AF. Other auto-detection parameters to aid in the detection of AF were 'relative pauses' which were triggered when an R-R interval was detected that had a duration 175% of the preceding R-R, and 'SVEs' (including isolated beats, couplets, triplets, and runs (PSVT)) which were triggered when an R-R interval was detected that was at least 25% shorter than the preceding R-R. Auto-detection parameters for 'absolute pauses' (R-R interval of >3 s), VT, VEs (including isolated beats, couplets, and triplets), tachycardias (>120 bpm), and bradycardias (<50 bpm) were also programmed. Aside from auto-detection parameters, the patient was able to make up to 5 patient-activated recordings (20 s pre- and 10 s post- button press) if they were symptomatic. The maximum length of monitoring was set as 7 days but was shortened if AF was detected sooner or patients were discharged early from hospital. When returned, the devices were analysed by a cardiac physiologist and a report sent to the requesting clinician. The R-TEST monitors were decontaminated following manufacturer's guidelines and local trust policy.

Data collection and handling

Anonymised data were entered into Microsoft Excel 2013 (Microsoft, Redmond, WA, USA) and analysed using SPSS Statistics 24.0 (SPSS Inc., Chicago, IL, USA). CHI squared statistics and Student's *t*-test were used as appropriate for non-parametric and parametric data respectively. A p value <0.05 was considered statistically significant.

Health economic modelling

A health economic model was developed to estimate the potential clinical and economic value delivered by R-TEST monitoring. Clinical and economic proxies were used to estimate the annual net benefit in terms of patient outcome and pounds Sterling (£). These proxies

included the number of secondary strokes, daily cost of inpatient care, number of inpatient bed days, device purchase and replacement every 3 years, pharmaceutical anticoagulation costs, and staff costs associated with R-TEST device fitting, monitoring, upkeep, and cleaning.

Ethical considerations

Approval to use anonymised patient data in this service evaluation was obtained from the local Caldicott Guardian. Full ethical approval was not required for this post hoc service evaluation.

Results

Demographics

One hundred patients were referred for an R-TEST monitor during the study period, of which 46% were female. The average age was 70 ± 11 years. Stroke was the presenting complaint in 83% patients, with the other 17% presenting with TIA. Inpatients made up 54% of the referrals. (Table 1A).

During the same time period (20th June 2019 and 3rd July 2020), the clinical service admitted 341 patients to the hospital with a non-haemorrhagic stroke. Of these, 87 had pre-existing AF prior to admission, with a further 60 cases of AF diagnosed on admission. In addition, 268 patients presented with a TIA. Of these, 31 had pre-existing AF and a further 16 AF diagnoses were made at the clinic. Thus, there were 194 non haemorrhagic stroke and 221 TIA patients who did not have known AF (415 patients in total).

AF detection

In the 100 stroke or TIA patients who did not have known AF and were referred for an R-TEST, AF was detected in 7 (8.4%) of 83 patients who had had a stroke and 1 (5.9%) of 17 patients with a TIA. Similarly, five (9.3%) of 54 inpatients and 3 (6.5%) of 46 outpatients were identified with paroxysmal AF following R-TEST monitoring. There was no statistical difference between those with AF detected or not in terms of age, gender or diagnosis (all $p > 0.05$) (Table 1B).

The AF burden in the 8 patients with AF detected ranged from 2 to 100%. The time of onset ranged from 0 to over 212 hours (Table 2).

Health economic analysis

The incidence of AF in patients enrolled in this study (5.9-8.4%) was used to derive a health economic model based on the annual number of NHS Highland patients presenting with stroke or TIA and not known to be in AF (415 in total) an estimated secondary stroke risk of 15 to 30% in patients with undiagnosed and untreated AF (9,10), and a 66% reduction in secondary stroke risk in AF patients following anticoagulation (18,19). Based on these figures, between 4 and 11 patients with undiagnosed and untreated AF are predicted to have a secondary stroke within 1 year of their initial stroke or TIA. Implementation of R-TEST monitoring and anticoagulation is predicted to prevent 3 to 7 of these secondary strokes (Figure 3). The intervention is therefore projected to deliver a reduction of 78-182 inpatient bed days and an annual gross savings of £31,200 - £72,800. Accounting for additional R-TEST purchase and replacement costs (n=8 devices at £2000 each), ECG data analysis and clinical time (at £20 / patient), as well as anticoagulant drug costs (£683.75 / patient), the achievable net savings is estimated at a maximum of £35,235.75 each year, or £5,033 per secondary stroke prevented (Table 3).

Discussion

This service evaluation has demonstrated that establishing a post-stroke prolonged monitoring service (up to 7 days) is feasible within existing staff resources in an NHS environment. Overall, we detected AF (or pAF) in 8% of monitored patients. In addition, to the improved patient care the service provides, our health economic analysis suggests a net financial benefit to the organisation.

Identifying asymptomatic AF and pAF has been identified in national guidelines as an important part of clinical care to reduce future strokes and associated morbidity and mortality (2). Nevertheless, robust guidance and data for physicians is lacking. In our study we identified AF or pAF in 8.4% of eligible patients with stroke and 5.9% in eligible patients with TIA. This is comparable with other data (5), however is lower than a recent audit from Kishore and colleagues (19) who detected new AF in 14.7% of eligible post ischaemic stroke patients. Detection rates may be even greater where even longer periods of monitoring are employed or where implantable devices such as Medtronic LINQ are used (17). Whilst Kishore et al (2020) detected a greater, but non-significant, number of new AF for inpatients versus outpatients (19.4 v 5.7 %, $p=0.07$), our detection rates were similar irrespective of inpatient/outpatient status (9.3 v 6.5 %). It is likely that the increased age (median age 76 years) and number of co-morbidities in their inpatient population contributed to the greater overall detection rates of new AF than that of the present study.

Interestingly, in the present study there were no differences in age and gender between patients with and without AF, which confirms that predicting patients at risk of AF is difficult.

The number of patients recruited to this pilot study was less than might be predicted to require an R-TEST in clinical practice. This is likely due to a variety of factors that were outwith the scope of this study to measure. These include patients already on a NOAC for other reasons e.g. venous thrombosis or pulmonary embolism, patients deemed too frail for NOAC, patients deemed unable to comply with monitoring and variation in practice including under-referral by clinicians. Under-referral by clinicians might be assumed to improve once the full clinical service is established. In the MonDAFIS study strokes were classified as ‘large artery atherosclerosis (27.5%), ‘cardioembolic’ (12.5%), ‘small artery occlusion’ (25.9%), ‘cryptogenic’ (31.5%) and ‘other’ (2.5%) (21). Thus, we might expect a future R-TEST service to have considerably more referrals. This potential increase in R-TEST referrals was included in health economic modelling, which assumed R-TEST referral for all stroke or TIA patients who did not have known AF (n=415 over the 1 year study period).

Economic analysis

This study demonstrated a high likelihood of cost effectiveness for the service. In addition to improving patient outcomes and quality of life by reducing the risk of secondary stroke, implementation of R-TEST monitoring based on results of this 100 person study are predicted to lead to measurable clinical benefits for NHS Highland, including reduced bed days and fewer secondary stroke patients as well as economic benefits in the form of net savings of up to £35,235.75 per year to the health board.

National context

The Royal College of Physicians National Clinical Guideline for Stroke 2016 recommends that, ‘people with ischaemic stroke or TIA who would be eligible for secondary prevention

treatment for atrial fibrillation (anticoagulation or left atrial appendage device closure) should undergo a period of prolonged (at least 12 hours) cardiac monitoring.’ and ‘people with ischaemic stroke or TIA who would be eligible for secondary prevention treatment for atrial fibrillation and in whom no other cause of stroke has been found should be considered for more prolonged ECG monitoring (24 hours or longer), particularly if they have a pattern of cerebral ischaemia on brain imaging suggestive of cardioembolism.’(2).

Despite inclusion in national guidelines and increasing evidence that asymptomatic AF post-stroke confers an increased risk of subsequent stroke, the provision of prolonged monitoring is not available in many centres. Prior to establishing the service in our centre, patients could not have prolonged monitoring and at best received a 24 h monitor. It is highly likely that AF and pAF were missed. Whilst we would need to perform a large-scale controlled trial to confirm this, a previous randomised controlled trial found that, after a 14-day follow-up, 18% of post ischaemic stroke patients that received standard practice + 7-days R-TEST monitoring were detected with pAF versus 2% in the standard practice control group (22). Nevertheless, there were several barriers to establishing this service at our hospital, including: a lack of suitable monitors; prolonged Holter monitoring being time-consuming for physiology staff. However, the availability of the R-TEST with automated analysis has greatly reduced the time taken to analyse recorded ECGs. The R-TEST analysis package for AF detection has been fully validated (23).

Service implementation

Despite high quality computer device analysis there were some challenges in establishing this service. Staff education, particularly on non-cardiology wards was important to ensure that devices were managed in an appropriate manner, including lead repositioning when displaced and removal and replacement of devices during bathing. Therefore, establishing the service

requires collaboration between departments and a willingness to deliver collaborative working to improve patient care. Despite these issues, after establishing R-TEST within the physiology department, the clinical service was relatively easy to implement.

For outpatients, the R-TEST was fitted either during the outpatient visit or remotely. In our region due to geographical factors we have established close working with general practitioners and all remote (non-urban) general practitioners have a practice-based cardiac external loop recorder either provided by the hospital or purchased locally. In the majority of cases the general practitioner fits the monitor with analysis and interpretation performed centrally in the physiology department. We have previously reported non-inferiority with this approach (24). This devolved service has proven of great worth with regard to patient convenience, reduced carbon foot print and more recently during the recent COVID-19 pandemic where the focus has to been to avoid unnecessary travel to the central hospital.

In the future we would expect that more patients would be referred as under-referral was acknowledged as an issue in this service evaluation. Those developing new services should be cognisant of this and the likelihood of increased demand as clinicians become familiar with new service.

Limitations

There are some limitations to our study: firstly, this was a single centre study but as it is the only stroke centre in our area it is highly likely that the participants are representative of the general UK stroke population and, therefore, it is likely that the results are generalisable. This was a small, short-term feasibility study and we therefore did not report recurrent strokes or longer-term outcomes. However, other larger studies are ongoing to address these questions. We did not report detailed morbidity data in our cohort or absolute stroke risk based on

CHA₂DS₂VASc score and all patients had suffered a stroke or TIA and all were eligible for anticoagulation if AF was detected.

Conflict of interest

This project was undertaken as part of a joint working agreement with Daiichi Sankyo Ltd who funded the R-TEST monitors only. Daiichi Sankyo had no input over the study design, participant recruitment, data collection and analysis, or content of this report and Daiichi Sankyo did not write the report.

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Author contributions

SJL led the study, wrote and edited the manuscript, and analysed results. DM, AG, and IM wrote and edited the manuscript and analysed results. KC, LM, NH, CG, SG, LC, GM, and AM conducted the study, collected, and analysed results.

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Figure legends

Figure 1 - Schematic of study design

Figure 2 - R-TEST monitor

Figure 3 - Estimated impact of R-TEST monitoring

Table 1A - Outcomes: Stroke vs TIA

Table 1B - Differences between patients with and without AF detected

Table 2 - Characteristics of patients diagnosed with new AF (or pAF)

Table 3 – Health economic analysis

Tables

Table 1A

| | All (n=100) | Stroke (n=83) | TIA (n=17) | <i>p</i> -value |
|--------------------|--------------------|--------------------|--------------------|-----------------|
| Age (years) | 70 ± 11 [48-89] | 71 ± 11 [48-89] | 65 ± 12 [48-89] | 0.053 |
| Female (n, %) | 46, 46% | 38, 46% | 8, 47% | 0.923 |
| AF Detected (n, %) | 8, 8% | 7, 8.4% | 1, 5.9% | 0.724 |
| In-patient (n, %) | 54, 54% | 52, 63% | 2, 12% | <0.001*** |

Table 1B

| | AF Negative (n=92) | AF Positive (n=8) | <i>p</i> -value |
|-------------------|-----------------------|----------------------|-----------------|
| Age (years) | 69 ± 12 [48-89] | 74 ± 8 [64-82] | 0.310 |
| Female (n, %) | 44, 48% | 2, 25% | 0.214 |
| Stroke (n, %) | 76, 82.6% | 7, 87.5% | 0.724 |
| In-patient (n, %) | 49, 53.3% | 5, 62.5% | 0.645 |

Table 2

| Patient | Age | Gender (M/F) | Stroke/ TIA | IP/OP | AF Burden (%) | Time from fitting of monitor to detection (days:hours) | Longest episode (hours: mins:secs) |
|----------------|------------|-------------------------|------------------------|--------------|------------------------------|---|---|
| 1 | 65 | M | Stroke | IP | 2 | 05:13 | 00:30:13 |
| 2 | 82 | M | Stroke | IP | 56 | 00:00 | 05:54:00 |
| 3 | 81 | M | Stroke | IP | 48 | 04:17 | 05:55 |
| 4 | 73 | F | Stroke | OP | 42 | 00:00 | 01:05 |
| 5 | 67 | F | Stroke | IP | 100 | 00:00 | 212:40:00 |
| 6 | 64 | M | TIA | OP | 4 | 01:21 | 01:45:00 |
| 7 | 85 | M | Stroke | OP | 92 | 00:00 | - |
| 8 | 76 | M | Stroke | IP | 16 | - | - |

Table 3

| Secondary care costs | | | |
|---|----------------------|---|---|
| Category | per stroke patient | | |
| | | no intervention (n=4-11 stroke patients) | with RTEST intervention (n=1-4 stroke patients) |
| bed days | 26 | 104-286 | 26-104 |
| Annual inpatient treatment cost / day | £400 | £41,600-£114,400 | £10,400 - £41,600 |
| | | | |
| | | | |
| Intervention costs | | | |
| Category | cost per patient (£) | total annual cost (£) | |
| RTEST device purchase and replacement (n=8) | 12.85 (n=415) | 5,333 | |
| RTEST data analysis and clinical time | 20 (n=415) | 8,300 | |
| Anticoagulant drug cost | 683.75 (n=25 - 35) | 17,093.75 – 23,931.25 | |
| | | | |
| Total annual intervention cost | | 30,726.75 – 37,564.25 | |