

Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis

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Scientific summary

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Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia. The prevalence of AF increases with age, and AF is more prevalent in men than in women. AF increases the risk of thromboembolic events, in particular stroke, with a fivefold increase in stroke risk in individuals with AF. Treatment of AF focuses on rhythm and rate control, and on prevention of stroke using oral anticoagulation therapy in individuals in whom return to sinus rhythm is unlikely. It is estimated that one-third of those with persistent AF will not have symptoms, and therefore that a first presentation of this might be a stroke. It is these individuals who would benefit most from a national screening programme for AF and subsequent anticoagulation therapy for stroke prevention. A national screening programme for AF would, however, involve a substantial investment of NHS resources, and the cost-effectiveness of such a programme would need to be established.

Objectives

The aim of this study was to assess the cost-effectiveness of different national screening strategies for AF in older adults. To achieve this aim we:

1. conducted a systematic review of diagnostic test accuracy (DTA) studies to determine the diagnostic accuracy of screening tests for detecting AF in adults who have not sought medical attention in a primary or community care setting on account of symptoms associated with AF, and to determine the diagnostic accuracy of screening tests in systematic opportunistic, targeted and population screening settings
2. updated a previous systematic review of screening strategies for AF to answer the following questions: (i) does systematic screening increase the detection of AF compared with routine practice?; (ii) what are the characteristics of those identified with AF by screening strategy?; (iii) which combination of screening strategy, screening population and test is the most effective at detecting AF compared with routine practice?; (iv) what are the potential safety issues and adverse events associated with individual screening programmes?; (v) how acceptable is the intervention to the target population?; and (vi) what are the costs associated with systematic screening for AF?
3. developed an economic model to compare the cost-effectiveness of different national screening strategies (including no screening) based on a review of previous economic evaluations of screening for AF and a review of recent literature on the prevalence, disease progression and risk profiles of AF and screening strategies relevant to a UK population-based screening setting.

Methods

Diagnostic test accuracy review

We searched for diagnostic cohort or case-control studies in MEDLINE, PreMEDLINE, EMBASE, The Cochrane Library, the Centre for Reviews and Dissemination and the Science Citation Index. Databases were searched without language or date restrictions until January 2015. The population of interest was individuals registered in primary care and/or presenting to primary care or community centres who had not sought medical attention on account of symptoms associated with AF. The index test could be any non-invasive test for AF that could be utilised in a primary care setting or in the community. The reference standard was a 12-lead electrocardiogram (ECG) interpreted by a cardiologist. Two reviewers screened the search results, extracted and checked the data and assessed the study quality using the Quality Assessment of Diagnostic Accuracy Studies – 2 (QUADAS-2) tool. Evidence synthesis was conducted by fitting a hierarchical summary receiver operating characteristic

(HSROC) model to estimate the relationship between sensitivity and specificity of the index tests, accounting for heterogeneity between studies. Heterogeneity was explored using preplanned subgroup analyses.

Review of randomised controlled trials comparing screening strategies

We updated and adapted a recent Cochrane review of screening strategies for AF. The population of interest was adults aged ≥ 40 years in whom population-based screening could be conducted. The interventions of interest were population-based, systematic (opportunistic, targeted or population) screening programmes for AF. We relaxed the requirement for confirmation of AF with a 12-lead ECG interpreted by a general practitioner (GP), specialist or suitably trained ECG technician because of a lack of studies. During the course of our review, we identified that the Health Information and Quality Authority (HIQA) in Ireland had published a health technology assessment (HTA) in which it had updated the Cochrane review from June 2012 to June 2015. We were also informed that the Cochrane review itself was being updated (currently undergoing peer review) and, with the assistance of the review authors, we updated this version of the review while expanding the scope as described above. Because the Cochrane update was restricted to randomised controlled trials (RCTs), we also restricted our review to RCTs. In addition, we updated the update by running searches from July 2015 to December 2015. Two reviewers screened the search results, extracted and checked the data and assessed the risk of bias. The study results were pooled using meta-analysis when sufficient evidence was available.

Economic evaluation

We reviewed the literature to identify previous economic evaluations of screening strategies for AF, using the NHS Economic Evaluation (NHS EED) and HTA databases from inception until close (end of December 2015), the Cochrane screening study review searches with economic filters and the Cost-Effectiveness Analysis (CEA) Registry. On the basis of this review, together with discussions with the project team, we developed an economic model consisting of a decision tree for the screening process and outcome and a discrete-time Markov model from a linked National Institute for Health Research HTA project, to provide the expected lifetime costs and benefits of anticoagulation therapy, if appropriate, given the outcomes of the screening model. We searched MEDLINE and EMBASE between 1 January 2000 and 22 January 2016 to identify studies providing information on the natural history of AF and screening for AF relevant to our economic model. The sensitivity and specificity of different screening tests came from the results of the DTA review meta-analysis. A probabilistic analysis is presented to reflect uncertainty in the model inputs. We report the mean total incremental costs, mean total incremental quality-adjusted life-years (QALYs) and mean incremental net benefit (INB) at a willingness to pay of £20,000 per QALY. To compare different screening strategies by age at first screen and number of repeated screens, we multiplied the per-person INB by the population size that will benefit (for a given age cohort). Costs and outcomes in future years over a lifetime time horizon were discounted at an annual rate of 3.5%.

Results

Diagnostic test accuracy review

We identified 15 studies of screening tests for the detection of AF, including a 12-lead ECG, single-lead ECGs, between 1- and 12-lead ECGs, pulse palpation, modified blood pressure monitors, photoplethysmography and two-stage testing. Screening tests varied in whether they were interpreted by a cardiologist, a GP, a nurse or an automatic algorithm, although evidence was not available for every test and interpreter combination and, when present, few observations were reported, leading to a lack of statistical power to detect meaningful differences. There was a high degree of variability between studies and a high level of uncertainty in the estimates of DTA. In general, most tests had a high sensitivity, in excess of 0.9. Specificity was, in general, lower than sensitivity for all of the tests. Tests with the highest diagnostic odds ratio (DOR) were the 12-lead ECG (regardless of interpreter), between 1- and 12-lead ECG (automatic or cardiologist interpretation), two-stage tests and single-lead ECG interpreted by a GP, with all of these tests having similar DORs.

In general, for a given interpreter, the results for the single-lead ECG were less accurate and more variable than ECGs with more than one lead. Nurse interpretation of single-lead ECGs performed similarly to single-lead ECGs with other interpretation methods, but nurse interpretation of 12-lead ECGs did not perform as well as other interpretation methods. Automatic interpretation did not have a consistent impact on test accuracy, with automatic interpretation of single-lead ECGs having a high sensitivity but variable specificity. In contrast, automatic interpretation of ECGs with more leads had good specificity but variable sensitivity. The different two-stage screening strategies all had very high specificity, but sensitivity was high only when a 12-lead ECG was used as the second-stage test.

Although photoplethysmography had very high test sensitivity, this estimate was based on a single study not based in primary care, in which the index test was rated as being at high risk of bias and the applicability of the patient selection was unclear. We are therefore cautious in interpreting the results from this screening test.

The results were robust to the sensitivity analyses, but we could perform only some of these because of a lack of data.

Review of randomised controlled trials comparing screening strategies

We identified five RCTs comparing screening strategies for AF; however, only two of these provided data that could be included in our review and only one was included for our primary outcome (the number of new AF diagnoses). The Screening for Atrial Fibrillation in the Elderly (SAFE) study therefore remains the main source of evidence on the comparative efficacy of different screening strategies for AF. Systematic population and systematic opportunistic screening strategies were found to be similarly effective, with an estimated 170 individuals needed to be screened to detect one additional AF case compared with no screening. There was no evidence that systematic screening targeted to high-risk individuals was effective compared with no screening.

Uptake of systematic population screening was typically around 50%, although uptake was as high as 70% in one study and there was variability in uptake between practices. Reasons for not attending for screening were varied, although older age and decreased mobility were commonly cited reasons. The proportion of individuals having their pulses checked under systematic opportunistic screening varied across studies (from 30% to 66%) and between practices within studies (from 8% to 93%). The proportion of individuals consulting with their GP was not reported, so it is unclear how much these uptake rates are driven by consultation rates, GPs offering pulse palpation and uptake of pulse palpation by individuals. Of those with an irregular pulse who did not have a previous diagnosis of AF, approximately 18% did not attend for an ECG test, although again this was variable across practices.

For systematic opportunistic screening, a greater proportion of the 75 newly identified cases were diagnosed outside the screening programme (44/75, 59%) than within it (31/75, 41%). This suggests that the full benefits seen in the systematic opportunistic arm may not be realised outside the context of a RCT.

There were no comparative studies of repeated screening strategies, and the majority of the evidence related to those aged 65–75 years.

Economic evaluation

Our results indicate that both systematic opportunistic and systematic population screening followed by directly acting oral anticoagulant therapy, where indicated, are likely to be cost-effective compared with no screening (current practice). Systematic opportunistic screening was more likely to be cost-effective than systematic population screening, as long as the proportion of flagged individuals who have their pulses checked observed in the SAFE study is realised in practice.

We found that photoplethysmography, modified blood pressure monitors and pulse palpation by a nurse were more likely to be cost-effective than other screening tests, because these are cheaper than other

screening tests while having adequate test sensitivity. This finding relies on the use of a 12-lead ECG diagnostic test interpreted by a GP (referred to a cardiologist when the diagnosis is unclear) in individuals with a positive screening test result.

For a single screen of a given age cohort, we found that strategies that use a higher age of screening were more likely to be cost-effective. However, when allowing for the possibility of repeated screening strategies with 5-year intervals, single screens were no longer found to be cost-effective; instead, an initial screen at age 65 followed by repeat screens every 5 years until age 80 years was found to be most likely to be cost-effective, provided that compliance with treatment does not decline with increasing age.

Although our model made many assumptions, we found that in general these were robust when tested in sensitivity analyses. If the uptake of pulse palpation in flagged patients is lower than that seen in the SAFE study, then a screening strategy in which individuals are invited by letter may be more appropriate. If the diagnosis rate of AF in the absence of screening is high, then the age at which to initiate screening is likely to be higher (70 years rather than 65 years).

Conclusions

A national screening programme for AF is likely to represent a cost-effective use of resources. Systematic opportunistic screening is more likely to be cost-effective than systematic population screening. Nurse pulse palpation or modified blood pressure monitors (if available) would be appropriate screening tests, followed by a diagnostic 12-lead ECG interpreted by a trained GP in those who screen positive, with referral to a cardiologist/specialist in cases in which the diagnosis is unclear. Implementation strategies to operationalise uptake of opportunistic screening in primary care should accompany any screening recommendations.

Research needs identified by this report are (1) the development and evaluation of strategies for the implementation of screening; (2) the evaluation of diagnostic performance against a reference standard of recent innovations (patches, smartphone/watch devices, iPads, hand-held devices) as well as devices used for other reasons that can also detect AF (pacemakers, implantable cardioverter defibrillator and implantable loop recorder devices), which may be of relevance to screening, particularly the detection of paroxysmal AF; (3) a comparative study to evaluate the long-term benefits of screening for chronic and paroxysmal AF and the yield from repeated screening tests; and (4) studies to replicate the DTA results for photoplethysmography and GP interpretation of 12-lead ECGs (with referral to a cardiologist/specialist in cases in which diagnosis is unclear) in a screening population.

Study registration

This study is registered as PROSPERO CRD42014013739.

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The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: <http://www.nets.nhr.ac.uk/programmes/hta>

This report

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