TITLE: Diagnostic accuracy of screening tests for atrial fibrillation

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BACKGROUND:

Target condition

Atrial fibrillation (AF) is the most common cardiac arrhythmia[1]. AF is categorised into four types:

(i) Paroxysmal AF (PAF) which is intermittent with episodes usually less than 48 hours, and stop without anti-arrhythmic treatment
(ii) Persistent AF which lasts more than a week if untreated with anti-arrhythmic drugs
(iii) Long-standing persistent AF which lasts more than a year
(iv) Permanent AF which is no longer corrected with anti-arrhythmic treatment

Symptoms of AF include: tiredness, breathlessness, dizziness, angina, and heart palpitations. The prevalence of AF increases with age[2, 3], and is slightly more prevalent in men than women[2]. Its population prevalence has been estimated to be 1.28%, and estimates of annual incidence range from 0.05% to 0.3%[2, 4]. AF is associated with a prothrombotic state that predisposes to stroke and thromboembolism, with a 5-fold increase in risk compared to those without AF[5]. Approximately 20% of all strokes are attributed to AF[6]. Approximately 1/3 of stroke patients die in the first 10 days, 1/3 recover in one month and 1/3 have disabilities needing rehabilitation making stroke the leading cause of adult disability. Prevention of stroke is the main objective in the management of AF. However, symptoms may be intermittent (paroxysmal) and are absent in around 20% of cases, which contributes to the under-diagnosis of AF in patients who are at a heightened risk of stroke, and who would benefit from prophylactic treatment. It has been estimated that 7000 strokes leading to approximately 2000 premature deaths could potentially be avoided every year through effective detection and treatment of AF[4].

Index test (s)

Any non-invasive screening test which can detect arrhythmia that could be used in a primary care or community setting to screen for AF. Possible examples include:

- Pulse palpation (assessment of pulse irregularity)
- 12-lead ECGs interpreted by primary care professionals or interpretative diagnostic software.
- ECGs with less than 12 leads interpreted by primary care professionals or computer programs. ECGs with fewer than 12-leads can have the advantage of avoiding the need for the patient to remove clothing and/or being quicker to perform.
- Finger probe. Similar to that used in general practice for pulse oximetry which uses the principle of photoplethysmography.
- Modified blood pressure monitors which detect pulse irregularities. These could either be used by people monitoring their own blood pressure at home or by primary care professionals. For example, a modified blood pressure monitor, WatchBP, which is modified to detect irregularity of pulse during blood pressure measurements, in combination with appropriate anticoagulation for those subsequently diagnosed with AF, has been suggested by NICE to have the potential to reduce the incidence of stroke.
- Mobile applications.

- Ambulatory ECG devices such as the Holter monitor, or an event recorder, worn for various lengths of time
- Any combination of the above

Rationale

It has been estimated that 7000 strokes leading to approximately 2000 premature deaths could potentially be avoided every year through effective detection and treatment of AF.

In this systematic review we will assess the accuracy of screening tests that can be carried out within a primary or community care setting.

We will consider the accuracy of the screening tests in three scenarios: opportunistic screening (screening patients when they present to primary care for different reasons), targeted screening (which will depend on risk factors that are predictive of AF) and systematic screening (general population screening).

OBJECTIVES:

To determine the diagnostic accuracy of screening tests (triage tests) for detecting AF in adult participants (≥18 years) who have not sought medical attention on account of symptoms associated with AF in a primary or community care setting.

Secondary objectives

To determine the diagnostic accuracy in opportunistic, targeted and systematic screening settings.

Investigation of sources of heterogeneity

- Age of participants
- Method of recruitment (i.e. whether all people were invited, whether people over a certain age or in a particular sub-group were invited for screening or whether people attending primary or secondary care for another reason were recruited)
- Setting
- Type of AF (paroxysmal, persistent, long-standing or permanent)
- Prevalence of AF, and prevalence of the four types of AF (paroxysmal, persistent, long-standing or permanent) in the population
- Frequency of screening (if multiple moment-in-time screening tests are identified)
- Length of monitoring (for ambulatory tests)
- Prevalence of co-morbidities (stroke, hypertension or cardiac disease) or risk of stroke ($CHADS_2$ or CHA_2DS_2-VASc score)
- Risk of AF (GRASP-AF score)
- Cut-off used

METHODS:

Criteria for considering studies for this review

Types of studies

Inclusion criteria:

Cross-sectional, case control and cohort studies, and RCTs where adults (≥18 years) are screened for AF using both an index test which could be administered in a primary or community care setting and

a comparator test. Studies may be performed in selected secondary or tertiary care settings as long as the case and non-case mix is likely to be similar to that seen during screening (for example outpatient day surgery) and the tests used could be administered in a primary or community care setting. In RCTs comparing screening strategies, we will regard each arm as a separate cohort.

We will only include studies from which either sensitivity and specificity or diagnostic two-by-two tables can be generated for a specific test, that is, studies that report data from which we can extract true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN).

To be included, the unit of analysis of the study must clearly have been the person.

Studies were only included when diagnostic test accuracy information was available for AF.

Exclusion criteria:

- Studies where participants only received one test.
- Studies with fewer than 40 participants.
- Prognostic studies.
- Studies where the unit of analysis is not the person (for example where different segments of ECGs from the same patient are analysed, so the same person can appear multiple times in a two-by-two table)
- Case-control studies where the controls all had another diagnosed arrhythmia.
- Studies in cardiology in- and outpatients, anticoagulant outpatients and intensive care (case and non-case mix likely to be different and/or inappropriate setting for screening)

Participants

Inclusion criteria:

Studies on adults (≥18 years) who are:

- Asymptomatic and who have not sought medical attention on account of symptoms associated with AF (palpitations, dizziness, angina, breathlessness).
- At increased risk of stroke (this includes patients who have had a prior stroke, but who are screened ≥3 months after the event).

Exclusion criteria:

Studies on any of the following populations:

- People <18 years old.
- People with symptoms of AF.
- People with co-morbidities or complications of AF such as stroke.
- People diagnosed with AF who have had curative treatment such as ablation or cardioversion.
- People with pacemakers/paced rhythms

Index tests

Inclusion criteria:

Any screening test that can detect arrhythmia that could be used and interpreted in a primary or community care setting to screen for AF.

Exclusion criteria:

Invasive tests or monitoring, for example REVEAL, and cardiac devices such as pacemakers or implanted cardiac defibrillators.

Target condition

AF.

Reference standards

12 lead ECG interpreted by a cardiologist.

Holter monitoring for at least 48 hours.

Search methods for the identification of studies

We will search MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, and Science Citation Index without language or date restrictions. Additional studies, including unpublished and grey literature, will be identified by screening reference list of retrieved studies and relevant review articles, and by searching trial registers. We will also search NHS EED, NICE Technology Appraisals and Clinical Guidelines.

Data collection and analysis

Selection of studies

Titles and abstracts will be screened independently by two reviewers (AM and GO) to identify potentially relevant studies. At title and abstract screening stage, studies will be excluded if the target condition is not AF, if the study is not a DTA study, if the study is performed exclusively in people with diagnosed or treated AF or if the index test is invasive, not possible in primary care, or does not detect arrhythmia. Full text articles of these studies will then be obtained and assessed for study eligibility using the full set of inclusion and exclusion criteria, this will also be performed independently by two reviewers (AM and GO). Conflicts at each stage will be resolved through discussion with a third reviewer (PD).

Data extraction and management.

Data extraction will be done by one reviewer and checked by a second.

The following data will be extracted:

- Authors, publication year, journal
- Study design
- Characteristics of study participants including age, gender and ethnicity
- Study inclusion and exclusion criteria
- Setting
- Prevalence of co-morbidities (for example hypertension, diabetes, renal failure, heart failure, heart disease, prior stroke or myocardial infarction) or risk of stroke $CHADS_2$ or CHA_2DS_2-VASc score) or risk of AF (GRASP-AF score)
- Prevalence of AF, prevalence of the four types of AF
- Method of participant recruitment
- Index test, including how and when the test was performed, frequency of screening and length of monitoring, and who performed and interpreted the test results
- Definition of a positive index test result/cut-off
- Reference test, including definition for disease positive
- If the readers of the index test and reference standard were blind to the results of the other test and other clinical information available to readers

- Number of missing or unavailable test results
- Number of TP, FN, FP and FN

To aid an economic evaluation we will also extract, where reported:

- The cost of the index test
- The length of time it takes to perform the index test
- Whether performing or interpreting the index test required special training

Assessment of methodological quality

We will use the QUADAS-2 tool to assess the quality of the identified studies (http://www.bris.ac.uk/quadas/).[7] Quality assessment will be done by one reviewer and checked by a second.

Statistical analysis and data synthesis

The numbers of TP, FN, FP and TNs will be extracted from each study. If results are reported for more than one threshold for a study, then we will extract data for each threshold reported.

Summary sensitivity and specificity values of each test at common thresholds will be calculated for each test compared to each of the reference standards. Positive and negative likelihood ratios and diagnostic odds ratios will also be calculated, together with possible ranges in positive and negative predictive values which will be based on estimates of disease prevalence. Confidence intervals for sensitivity, specificity, likelihood ratios and diagnostic odds ratios will be displayed using forest plots.

Formal analyses will use hierarchical summary ROC models. These statistically rigorous approaches allow estimation of summary sensitivity, specificity, likelihood ratios and diagnostic odds ratios with associated confidence intervals or regions. We will adapt these models to allow for the incorporation of results from studies reporting results on multiple thresholds. They also allow estimation of summary ROC curves and prediction regions for the true sensitivity and specificity in a future study.

Ideally, all diagnostic tests will have been compared to the same gold-standard test. In practise this may not be the case, however as long as there is a connected network of diagnostic test comparisons, then network meta-analysis methods will be adapted to estimate ROC curves for all tests relative to a single gold standard reference test.

Investigations of heterogeneity and Sensitivity analyses

We will inspect between study variance for evidence of heterogeneity. We anticipate that heterogeneity will be an issue with this review, and will explore possible explanations of heterogeneity through subgroup analyses and the incorporation of covariates, including study design, study year, age, setting, type of AF, method of recruitment into the study (targeted, opportunistic or systematic), and stroke risk-score and risk-of-bias indicators (see above).

Sensitivity analyses will be performed to the inclusion/exclusion of studies assessed to be at high risk of bias.

Assessment of reporting bias

There is limited evidence of publication bias in test accuracy research. Typical methods for assessing reporting bias may be misleading if applied to meta-analyses of test accuracy.[8] Therefore we will not assess reporting bias.

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Department of Health Disclaimer:

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

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ATRIAL FIBRILLATION SCREENING STRATEGIES – SYSTEMATIC REVIEW PROTOCOL

PROTOCOL AUTHORS: George Okoli, Alexandra McAleenan, Philippa Davies, Julian Higgins, Reecha Sofat, Gene Feder, Aroon Hingorani, Peter Bryden, Alison Richards, Nicky J. Welton

BACKGROUND

Description of condition: Atrial fibrillation (AF) is the most common cardiac arrhythmia[1]. Symptoms include: tiredness, breathlessness, dizziness, angina, and heart palpitations. The prevalence of AF increases with age[2, 3], and is slightly more prevalent in men than women[2]. Its population prevalence has been estimated to be 1.28%, and estimates of annual incidence range from 0.05% to 0.3%[2, 4]. AF is associated with a prothrombotic state that predisposes to stroke and thromboembolism, with a 5-fold increase in risk compared to those without AF[5]. Approximately 20% of all strokes are attributed to AF[6]. Approximately 1/3 of stroke patients die in the first 10 days, 1/3 recover in one month and 1/3 have disabilities needing rehabilitation making stroke the leading cause of adult disability. Prevention of stroke is the main objective in the management of AF. However, symptoms may be intermittent (paroxysmal) and are absent in around 20% of cases, which contributes to the under-diagnosis of AF in patients who are at a heightened risk of stroke, and who would benefit from prophylactic treatment. It has been estimated that 7000 strokes leading to approximately 2000 premature deaths could potentially be avoided every year through effective detection and treatment of AF[4].

Description of interventions: The interventions in this review are systematic screening strategies, including population, targeted (e.g. age range), or opportunistic (e.g. given a GP consultation together with age and other risk factors) screening programmes, compared with routine practise (no screening) or with each other. Our focus is on screening strategies conducted within a primary care setting, but we will not exclude studies on the basis of this and will summarise evidence on screening within a secondary care setting.

Review objective: To update the Cochrane review of screening strategies for AF[7].

Review questions: This review aims to answer the following questions:

1. Does systematic screening increase the detection of AF compared to routine practice?
2. What are the characteristics of those identified with AF by screening strategy?
3. Which combination of screening strategy, screening population and test is the most effective at detecting AF compared to routine practice?
4. What are the potential safety issues and adverse events associated with individual screening programmes?
5. How acceptable is the intervention to the target population?
6. What are the costs associated with systematic screening for AF?

PICO FRAMEWORK

***Population*:** In line with the Cochrane review, the population of interest is adults (≥40 years old), of any sex (epidemiological data has showed that AF is extremely uncommon below the age of 40 years).

***Interventions of interest*:**

- Systematic population screening for AF

- Systematic targeted screening for AF
- Systematic opportunistic screening for AF

Where a diagnosis of AF was defined as a positive reading using a single lead, 3-lead, or 12-lead ECG, or a 24hour or more continuous ambulatory ECG, interpreted by a physician.

***Comparator*:** Routine practise (i.e. no screening for AF) where a diagnosis of AF was defined as a positive reading using a single lead, 3-lead, or 12lead ECG, or a 24hour or more continuous ambulatory ECG, interpreted by a physician. We will also include studies comparing two or more screening strategies without a "no screening" arm.

***Outcomes*:**

Primary Outcome

The primary outcome is the proportion of new cases of AF detected. This will only be calculated using data from studies that provide a clear denominator. In the case of randomised controlled trials, this would be the numbers of people in the intervention or control groups, making sure that patients with a prior AF diagnosis are excluded from the numerator. We will report the proportion of new AF cases detected for (i) all invited (prior AF cases included in denominator) and also (ii) all those without a prior AF diagnosis.

Secondary Outcomes

The secondary outcomes cover those of the original Cochrane review[7], and others important for our economic evaluation:

1. Acceptability of systematic screening programmes within the target population. This will be examined in three ways: the level of uptake achieved, feedback elicited from the participants and health professionals involved, and a description of any direct costs associated with screening that were borne by the person to whom the screening programme was offered.
2. Adverse events associated with systematic screening. The rate and severity of complications or adverse events associated with ECG or other forms of AF testing will be recorded. Psychological distress, change in quality of life and impact on well-being were included if these outcomes were measured using a validated scale. Adverse events related to treatment following a diagnosis of AF were excluded.
3. Costs associated with systematic screening programmes for AF – Only direct costs from the perspective of the healthcare provider will be included in the analysis of this outcome. Where possible, a description of the operational and training costs associated with screening will be provided along with the incremental cost of screening and cost per additional case detected compared with a policy of no screening.
4. Prevalence of AF with and without screening, where the denominator can be clearly determined. Also, prevalence of previously diagnosed AF in the screening and no screening groups.
5. Patient characteristics of those detected with AF (age, sex, clinical history, CHA2DS2-VASC score, AF type)

STUDY SELECTION

Inclusion criteria: All randomised controlled trials (RCT), cluster randomised controlled trials (cluster-RCT), quasi-randomised controlled trials, interrupted time series and controlled before-and-after

studies comparing systematic population, targeted, or opportunistic screening strategies for AF with routine practise (no screening). Studies comparing two or more of these screening strategies for AF will also be eligible for inclusion, even if there is no routine practise (no screening) arm.

Exclusion criteria: Observational studies and studies not comparing the interventions of interest.

Search and screening methods for study identification: Since we aim to update the Cochrane review, we will search the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, MEDLINE (Ovid) (including MEDLINE in-process) [March 2012 to 13th August 2015), EMBASE and EMBASE Classic (Ovid) [Week 12 2012 to 13th August 2015), CINAHL (via EBSCO [June 2012 to 13th August 2015), CBA and ITS studies. Relevant studies from June 2012 to 17th August 2015 will be searched in trials registries and websites such as ClinicalTrials.gov, ISRCTN Registry, Stroke Trials Directory, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), Clinical Trials Registry of the University Medical Centre Freiburg, European Union (EU) Clinical Trials Register, Iranian Registry of Controlled Trials, Japanese NIPH Clinical Trials Registry, UMIN-CTR (Japan), Nederland's Trial Register, Pan African Clinical Trials Registry, Sri Lanka Clinical Trials Registry, Australian New Zealand Clinical Trials Registry, Chinese Clinical Tries Registry, Brazilian Clinical Trials Registry, Korean Clinical Research Information Service, Clinical Trials Registry of India, and the websites of Eurostroke (European Stroke Conference), EHRA and ACC. Where required, we will contact lead authors and investigators for information about published and unpublished studies that may be relevant. There will be no language restrictions.

Identified literature will be screened by two reviewers, applying the eligibility criteria using a two stage sifting approach to review literature title and abstracts, and full texts. The number of excluded literature will be recorded at each screening stage. A PRISMA diagram will be produced and reasons for exclusion will be recorded when screening at the full text stage. Any disagreement between the two reviewers will be discussed and resolved with the involvement of a third reviewer.

Because the Cochrane review excluded comparative studies that did not have a "no screening" control, we will search the list of excluded studies from the Cochrane review and re-assess them for inclusion in our review.

Note: During the course of our review, an update to the Cochrane review was published. We judged this update to be similar to our review but not identical as our inclusion criteria were broader since we planned to also include studies that directly compared different screening strategies and not just those that compared screening strategies with routine care (no screening). Furthermore, we planned to follow the original Cochrane review protocol and include interrupted time series and controlled before-and-after studies, whereas the Cochrane review update restricted to RCTs only because the original Cochrane review found only RCTs. We contacted the review update team to access their list of included and excluded studies and having confirmed from the team that all head to head comparison studies between systematic screening types would have been picked by their searches, and listed as excluded studies following screening, we were confident to use their list of included and excluded studies since these studies would have been captured in our review. We therefore decided not to screen the records from our searches. Since the Cochrane review update included only RCTs, we assumed that no interrupted time series or controlled before-and-after studies would have been published during the period of the review update searches. However, we identified a few months that were not covered by the update searches i.e. April to May 2012 and July to August 2015. We therefore ran searches covering these periods, utilizing our originally specified search protocols. We however extended our searches to cover up to December 2015. The records from these periods were then screened as per our protocol.

DATA EXTRACTION

Data will be collected according to the PICO framework as already explained using a piloted extraction form. Data extraction and quality assessments will be conducted by one reviewer and then reviewed by a second reviewer. Any disagreements will be recorded and resolved with the involvement of a third reviewer.

Assessment of risk of bias: The risk of bias of selected studies will be assessed at study and outcome levels using the Cochrane Collaboration suggested risk of bias assessment tool for Effective Practice and Organisation of Care (EPOC) reviews involving RCTs (including cluster and quasi types), non-RCTs, controlled before-and-after studies, and interrupted time series. The result of each assessment will be presented per domain or question since both the Cochrane Collaboration and PRISMA statement recommend against the use of summary scores for describing an overall risk of bias. Abstracts that are assessed to meet the study eligibility criteria for inclusion will be subjected to data extraction only and not assessment for risk of bias due to a potential lack of information to enable judgment in some domains.

Heterogeneity: Effect modifiers stated in each study will be documented. In compliance with the Cochrane Collaboration, potential sources of heterogeneity anticipated to be of importance in the review are:

- At study level:
  - Demography of the study population
  - Settings from which study population has been sampled
  - Interpretation of tests (differences in the ability of the physicians, technicians and nurses)
  - Type of AF
  - Method of confirming diagnosis

- At study participant's (individual) level:
  - Comorbidities
  - Type of AF
  - Method of confirming diagnosis

DATA ANALYSIS

We will estimate the relative efficacy and safety of AF screening programs. Our methods will closely follow a previously conducted Cochrane review of systematic screening for the detection of AF.

Study specific characteristics and outcome measures will be tabulated. Risk of bias assessments will be presented using the Cochrane risk of bias tool. A narrative description of the results will be given. Relative effects for binary outcomes (proportion of new AF cases) will be summarised using odds ratios. The number needed to screen (NNS) in order to detect one additional new case of AF within the population will be calculated from the overall difference in the numbers of AF cases. If sufficient data is reported, we will estimate prevalence and incidence of AF by type (paroxysmal, persistent, permanent), and the proportion of AF that is asymptomatic. Relative effects for continuous outcomes will be reported as mean differences if measured on a comparable scale, and standardised mean differences otherwise.

If multiple studies are identified that are sufficiently similar in design, results will be combined in a meta-analysis. We will consider different types of screening programme to be different "interventions", and perform network meta-analysis[9] if the studies form a connected network of intervention comparisons. A network diagram will be drawn for each outcome. A Bayesian approach to estimation will be taken using Markov chain Monte Carlo (MCMC) simulation in WinBUGS[10]. Convergence of the MCMC simulation will be assessed using the Brooks Gelman Rubin statistics.

Fixed effect models will be fitted, and also random effects models if sufficient data available. Choice between fixed and random effects models will be based on model fit, between study variance and I^2. Model fit will be assessed using the posterior mean residual deviance, and the Deviance Information Criterion (DIC); a difference of 3 or more points will be considered meaningful. If perform network meta-analysis, then we will explore inconsistency in the model using model fit statistics as described above. Statistical heterogeneity and inconsistency will be investigated by considering clinical heterogeneity of the populations across included studies.

If sufficient data is available, subgroup analysis will be performed on the following:

1. Over 65 years of age.

2. Aged 65 to 75 years versus > 75 years.

3. Men versus women.

4. Different ethnic groups, if reported.

5. Different socioeconomic groups, if reported.

6. Community versus specialist setting.

Sensitivity analysis will be performed to the exclusion of trials with a high risk of bias.

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Department of Health Disclaimer:

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

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