Protocol HTA Technology Assessment Report

October 2009

08/45/01 HTA TAR

## 1. Title of the project

Echocardiography in newly diagnosed atrial fibrillation patients

## 2. Name of TAR team and project 'lead'

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## 3. Plain English Summary

Cardiac arrhythmias affect the heart, causing an irregular heartbeat. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.[1] AF is more common in older people. At age 80–89 years, almost 9% of people have AF.[1] It can occur in both men and women, but is more common in men. AF does not always cause symptoms, but may cause palpitations, chest pain, dizziness, or fainting.[1] An irregular heartbeat makes the heart less efficient at circulating blood around the body. This can increase the risk of blood clots developing within the circulatory system. If left untreated, AF is a significant risk factor for stroke and other morbidities.[1] AF can be caused by other medical conditions, such as heart disease or hypertension, or may occur following surgery.[1]

Transthoracic echocardiography (TTE) is a procedure that allows imaging of the heart and blood flow.[2] By undergoing echocardiography, cardiac abnormalities can be diagnosed earlier than would be possible if symptoms were left to develop.[1] Currently, only selected patients with AF have TTE. These patients are selected because their clinical symptoms mean that heart disease is suspected, or because treatment planning requires the further information that TTE can provide.[1]

The aim of this report is to evaluate whether all newly diagnosed AF patients should have TTE, rather than just the selected AF patients for whom TTE is currently recommended.

## 4. Decision problem

*4.1 Purpose of assessment*

The assessment will address the question "What is the clinical and cost effectiveness of performing a routine echocardiogram in all newly diagnosed atrial fibrillation (AF) patients in preventing complications arising from AF, in comparison with current practice of selective testing?"

*4.2 Clear definition of the intervention (e.g. licensed indications, dosages being considered)*

Echocardiography is an ultrasound imaging procedure used to examine the heart. Transthoracic echocardiography (TTE) is non-invasive echocardiography, performed by placing the ultrasound device across the chest.[1] TTE images cardiac structures including all four cardiac valves, cardiac walls and the velocity of blood flow in the heart by using beams of sound at frequencies of 2.5-5MHz.[2]

TTE may be used to refine clinical risk stratification for antithrombotic therapy.[1] It can also be used to assess the risk of recurrent AF following cardioversion, or to assess the risk of developing postoperative AF.[1]

*4.3 Place of the intervention in the treatment pathway(s)*

The assessment will investigate the effects of performing routine TTE in all newly diagnosed AF patients. In this case, the intervention would be performed soon after diagnosis of AF, without requiring symptoms of further pathology to be present. If data are available the cost effectiveness of targeting TTE in sub-populations of newly diagnosed AF patients will be undertaken.

*4.4 Relevant comparators*

The comparator for all intervention strategies will be current practice. Treatment for AF depends on the type of AF diagnosed, as well as comorbidities, drug contraindications and patient preference.[1] Pharmacological treatments include antithrombotic therapy, antiarrhythmic agents, beta-blockers or rate-limiting calcium antagonists. Other treatments may include electrical cardioversion or surgical procedures (such as pacemaker therapy, arrhythmia surgery, catheter ablation or use of atrial defibrillators).[1]

*4.5 Population and relevant sub-groups*

The main focus of the assessment will be newly diagnosed AF patients for whom TTE is not currently recommended. This will include patients with AF for whom the need to initiate anticoagulation therapy has already been decided on clinical criteria, as NICE guidelines for AF[1] state that TTE should not be routinely performed in this circumstance. As stated in section 4.3, if data are available the cost effectiveness of targeting TTE in sub-populations of newly diagnosed AF patients will be undertaken. This could allow some sub-groups to receive TTE whilst others do not.

The assessment will also evaluate not using TTE in any newly diagnosed AF patients. This will allow an analysis of the cost effectiveness of TTE in patients currently meeting the criteria for recommended TTE in the NICE guidelines for AF.[1] These comprise:

Younger patients for whom a baseline echocardiogram is important for long-term management;

Patients for whom cardioversion (electrical or pharmacological) is being considered;

Patients in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management;

Patients in need of clinical risk stratification for antithrombotic therapy.

Sub groups
Where data are available, the assessment will consider separately patients with AF for whom the need to initiate anticoagulation therapy has already been decided on clinical criteria.

Where data are available, the assessment will consider separately those patients for whom AF was diagnosed when they presented with associated medical conditions (heart failure, stroke or thromboembolism), as opposed to patients with AF as primary diagnosis whether asymptomatic, or based on symptoms not requiring hospital visit.

Where data are available, the assessment will consider separately patients with paroxysmal, persistent or permanent diagnoses of AF.

*4.6 Key factors to be addressed (e.g. clinical and cost outcomes, further considerations, problematic factors)*

The objectives of the review are:
to investigate (by systematic review) the prevalence of clinically important pathology in AF;
to investigate (by systematic review) the diagnostic accuracy of TTE for these abnormalities;
to estimate the potential benefits and harms due to altered treatment based on results of TTE;
to estimate the incremental cost effectiveness of routine TTE for newly diagnosed compared with current practice of TTE in selected AF patients;
to estimate the incremental cost effectiveness of providing routine TTE to subgroups within the newly diagnosed AF patient population (where data are available).

## 5. Report methods for synthesis of evidence of clinical effectiveness

Two reviews (1 - prevalence of clinically important pathology in AF; 2 - diagnostic accuracy of TTE for these abnormalities) of the evidence will be undertaken systematically following the general principles recommended in the QUOROM statement.[3]

Population
The population will be the same for both reviews.
Inclusion
Newly diagnosed AF patients. Diagnosis of AF is confirmed by electrocardiogram (ECG), which may be standard ECG, 24-hour ambulatory ECG or event recorder ECG. The population for this review will be those AF patients for whom TTE is not currently recommended. This will include patients with AF for whom the need to initiate anticoagulation therapy has already been decided on clinical criteria,

Sub groups
Where data are available, the assessment will consider separately subgroups of Patients currently meeting the criteria for recommended TTE in the NICE guidelines for AF,[1] as routine TTE would not alter practice for these patients. These comprise: younger patients for whom a baseline echocardiogram is important for long-term management; patients for whom cardioversion (electrical or pharmacological) is being considered; patients in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management; patients in need of clinical risk stratification for antithrombotic therapy.

Where data are available, the assessment will consider separately patients with AF for whom the need to initiate anticoagulation therapy has already been decided on clinical criteria, for whom NICE guidelines for AF[1] state that TTE should not be routinely performed.

Where data are available, the assessment will consider separately those patients for whom AF was diagnosed when they presented with associated medical conditions (heart failure, stroke

or thromboembolism), as opposed to patients with AF as primary diagnosis whether asymptomatic, or based on symptoms not requiring hospital visit.

Where data are available, the assessment will consider separately patients with paroxysmal, persistent or permanent diagnoses of AF.

Study selection and data extraction strategy
For both reviews, study selection will be made by one reviewer. The following publication types will be excluded: animal models, preclinical and biological studies, editorials, opinion pieces, studies only published in languages other than English, reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality. Data will be extracted independently by one reviewer using a standardised data extraction form and checked by another. Discrepancies will be resolved by discussion.

Search strategy
The search strategy for both reviews will comprise the following main elements: Searching of electronic databases, Contact with experts in the field, Scrutiny of bibliographies of retrieved papers and Citation Searching.

Databases:
Electronic databases: including MEDLINE; Medline in Process (for latest publications); EMBASE; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases; NIHR Clinical Research Network Portfolio database; NRR (National Research Register) Archive; Web of Science Proceedings; Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website and relevant conference proceedings.

The draft search strategy is shown in Appendix 1.

*5.1 Review of prevalence of pathology in AF patients*
Prevalence of pathology in AF patients will be sought from epidemiological studies.
Pathologies will be restricted to those that could be identified by TTE. These include left ventricular impairment or hypertrophy, weakened heart muscle/cardiomyopathy, heart valve problems, aortic aneurysm, blood clots, tumours, pericarditis, pulmonary hypertension. Quality assessment will depend on types of studies identified, but is likely to be based on the STROBE statement (see Appendix 2).[4] Data will be tabulated and discussed in a narrative review.

*5.2 Review of diagnostic accuracy of TTE*
Diagnostic accuracy of TTE will be sought from studies comparing detected pathology from TTE or other diagnostic tools. Outcomes of sensitivity (proportion of true positives) and specificity (proportion of true negatives) will be identified. Studies looking at prognostic accuracy will also be sought, that is, TTE results predicting later cardiovascular events. Quality assessment will depend on types of studies identified, but is likely to be based on QUADAS (see Appendix 2).[5] Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes.

*5.3 Further information needed*
Further clinical data needed for economic modelling will be sought from clinical guidelines, advice from clinical experts or systematic reviews.

If studies of prognostic accuracy (i.e. the ability of TTE to predict cardiovascular events) are not available, it will be necessary to find data on the risk of cardiovascular events arising from each clinically important pathology.

Considering how each clinically important pathology is treated, details of current NHS practice, and data on the benefits and harms of these treatments in the relevant population will be needed.

## 6. Report methods for synthesising evidence of cost-effectiveness

A systematic review of the existing literature studying the cost-effectiveness of echocardiography in newly diagnosed AF patients will be undertaken. In addition, a new economic model will be developed to compare a treatment strategy which incorporates early use of echocardiography for all newly diagnosed AF patients, with a strategy that incorporates early use of echocardiography only in patients outlined by the NICE AF guideline (i.e. current practice).

### *6.1 Identifying and systematically reviewing published cost effectiveness studies*

The sources detailed in Section 5 will be used to identify studies of the cost effectiveness of echocardiography for newly diagnosed AF patients. An economic search filter will be integrated into the search strategy to identify relevant studies. Identified economic literature will be critically appraised and assessed using the Drummond checklist.[6] Existing cost effectiveness analyses will also be used to identify sources of evidence to inform structural modelling assumptions and parameter values for the economic model.

### *6.2 Development of a health economic model*

A de novo economic evaluation will be constructed, it is likely that a Markov model approach will be used, and the primary outcome from the model will be an estimate of the incremental cost per additional quality adjusted life year (QALY) gained associated with use of echocardiography for newly diagnosed AF patient. The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease and potential mortality. The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%. Modelling assumptions will be taken from the literature, supplemented by clinical expert opinion where necessary. In the absence of direct data, QALYs will have to be selected from those included in publications for studies of treatments for AF in fairly general populations in the UK, such as radio-frequency catheter ablation versus anti-arrhythmic drug therapy.[7]

The model structure will be determined in consultation with clinical experts. The different types of AF (paroxysmal, persistent and permanent), the different treatment strategies (rate control and rhythm control) and the associated treatment pathways will need to be taken into account. The model will include estimates of the difference that echocardiography makes to ensuring appropriate care for the different types of AF patients, as well as costs of the intervention and subsequent downstream costs associated with appropriate and inappropriate care. This will enable an analysis of whether early echocardiography is cost effective for different patient groups.

Ideally, health related quality of life estimates will be available from the reviewed literature. In the absence of such evidence, the economic model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model. National sources (e.g. NHS reference costs[8], national unit costs[9], British National Formulary[10]) as well as the reviewed literature will be used to estimate resource use and costs for use in the economic model.

It is anticipated that there may be limited evidence for some of parameters that will be included in the economic model. Therefore the uncertainty around the parameter estimates will be modelled to take account of this. The uncertainty in the central value for each required parameter will be represented by a distribution, enabling probabilistic sensitivity analysis to be undertaken on the model results. This will allow an assessment of the uncertainty to be made, and the results will be interpreted accordingly. Through expected value of information analysis and expected value of perfect parameter information analysis we will identify whether further research is valuable, and in which areas further research is likely to be particularly valuable.

## 7. Expertise in this TAR team

TAR Centre

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the effectiveness and cost effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Clinical Excellence.

## 8. Competing interests of authors

Nick Latimer previously worked on a project about dronedarone funded by Sanofi-Aventis. To date, dronedarone has not been considered by NICE for use in the NHS.

## 9. Timetable/milestones

| **Milestone** | **Date** |
|---|---|
| Draft protocol | 31st July 2009 |
| Final protocol | 23rd October 2009 |
| Progress report | August 2010 |
| Assessment report | September 2010 |

TAR Team

Emma Simpson, Research Fellow, ScHARR: has experience in systematic reviews of health technologies including involvement in Heath Technology Assessment Reports. She will lead the project and undertake the systematic reviewing of clinical effectiveness and has been involved in developing the protocol.

Nick Latimer, Research Fellow, ScHARR: has experience in operational research techniques. He has been involved in developing the protocol.

Patrick Fitzgerald, Research Fellow, ScHARR: has experience in operational research techniques. He will undertake the review of cost effectiveness and development of the cost-effectiveness model.

Matt Stevenson, Operational Research Analyst, ScHARR: will supervise the development of the cost effectiveness model.

Anna Cantrell, Information Officer, ScHARR: has experience of undertaking literature searches for the ScHARR Technology Assessment Group systematic reviews and other external projects. She will develop the search strategy and undertake the electronic literature searches.

Edith Poku, Research Associate, ScHARR: will assist in the systematic reviewing of clinical effectiveness.

Andrea Shippam, Project Administrator: will assist in the retrieval of papers and in preparing and formatting the report.

Dr Navroz Masani, Consultant Cardiologist, Department of Cardiology, University Hospital of Wales, Heath Park, Cardiff CF14 4XW: will act as a clinical advisor.

Professor Gregory YH Lip, Consultant Cardiologist and Professor of Cardiovascular Medicine, University Department of Medicine, City Hospital, Birmingham B18 7QH: will act as a clinical advisor.

## 10. Appendices

### Appendix 1 Draft search strategy

The search strategy below was developed on Medline (OVID), a similar search will be performed on the other databases.

Prevalence of pathology in Atrial Fibrillation patients

1. Atrial Fibrillation/
2. af.tw.
3. atrial fibrillation.tw.
4. or/1-3
5. Ventricular Dysfunction, Left/
6. Hypertrophy, Left Ventricular/
7. left ventricular impairment$.tw.
8. left ventricular hypertrophy.tw.
9. Cardiomyopathies/
10. heart valve problem$.tw.
11. "Heart Valve Diseases"/
12. Aortic Aneurysm/
13. aortic aneurysm.tw.
14. blood clot$.tw.
15. Pericarditis/
16. pericarditi$.tw.
17. Neoplasms/
18. tumour$.tw.
19. or/5-18
20. 4 and 19
21. exp Epidemiologic Studies/
22. exp Epidemiology/
23. epidemiology.tw.
24. exp Prevalence/
25. prevalence.ti.
26. exp Incidence/
27. incidence.ti.
28. or/21-27
29. 20 and 28

The above search combines terms for atrial fibrillation (1-3) with terms for the different pathologies that could occur in atrial fibrillation patients and can be identified by TTE (5-18) with terms to identify epidemiological studies.

Diagnostic Accuracy of Transthoracic Echocardiography

1. Atrial Fibrillation/
2. af.tw.
3. atrial fibrillation.tw.
4. or/1-3
5. Echocardiography/
6. echocardiograp$.tw.
7. transthoracic echocardiography.tw.
8. tte.tw.
9. or/5-8
10. 4 and 9
11. exp "Sensitivity and Specificity"/

12. sensitivity.tw.
13. specificity.tw.
14. ((pre-test or pretest) adj probability).tw.
15. post-test probability.tw.
16. predictive value$.tw.
17. likelihood ratio$.tw.
18. or/11-17
19. 10 and 18

The above search combines terms to describe atrial fibrillation (1-3) and terms to describe transthoracic echocardiography (5-8). The search is e combined with a search filters designed to retrieve diagnostic studies (11-17) to retrieve information on the diagnostic accuracy of transthoracic echocardiography.

**Appendix 2 Draft data extraction**

Forms to be adapted from the following

QUADAS (quality assessment of studies of diagnostic accuracy)[5]

Was the spectrum of patients described in the paper and was it chosen adequately?
Were selection criteria described clearly?
Was the method of population recruitment consecutive?
Was the setting of the study relevant?
In light of current technology, was the reference standard chosen appropriate to verify test results?
Was there an abnormally long time period between the performance of the test under evaluation and the confirmation of the diagnosis with the reference standard?
Was the execution of the index test described in sufficient detail to permit replication of the test?
Was the execution of the reference standard described in sufficient detail to permit replication of the test?
Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis?
Did all patients receive the same reference standard regardless of the index test result?
Were the results of the index test incorporated in the results of the reference standard?
Were the index test results interpreted blind to the results of the reference standard?
Were the reference standard results interpreted blind to the results of the index test?
Was clinical data available when test results were interpreted?
Were uninterpretable/indeterminate/ intermediate results reported and included in the results?
Were reasons for drop-out from the study reported?

STROBE (Strengthening the reporting of observational studies in epidemiology)[4]

| | | |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| | | (*b*) Describe any methods used to examine subgroups and interactions |
| | | (*c*) Explain how missing data were addressed |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| | | (*e*) Describe any sensitivity analyses |
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | | (b) Give reasons for non-participation at each stage |
| | | (c) Consider use of a flow diagram |
| Descriptive data | 14 | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| | | (b) Indicate number of participants with missing data for each variable of interest |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| Outcome data | 15 | *Cohort study*—Report numbers of outcome events or summary measures over time |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| Main results | 16 | *a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | | (*b*) Report category boundaries when continuous variables were categorized |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

## 11. References


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