Screening for Atrial Fibrillation in People aged 65 and over

A report

for the National Screening Committee

May 2014

Solutions for Public Health

www.sph.nhs.uk

This report has been compiled by

Dr Martin Allaby, Consultant in Public Health

This work was undertaken by Solutions for Public Health (SPH) who received funding from the Department of Health via the National Screening Committee. Views expressed in this publication are those of the author and not necessarily of the Department of Health.

Solutions for Public Health

4150 Chancellor Court

Oxford Business Park South

Oxford

OX4 2GX

Tel: +44 (0)1865 334700

www.sph.nhs.uk

Contents

Introduction

1. This paper reviews screening of people aged 65 years and over for atrial fibrillation (AF) against the UK National Screening Committee Criteria for appraising the viability, effectiveness and appropriateness of a screening programme (National Screening Committee 2003). It is based on a literature search conducted by the National Screening Committee in July 2010, with an update using the same search strategy in December 2011. People with AF have an irregular pulse, a clinical sign which is easily detected and can lead to diagnosis or exclusion of AF through an electrocardiogram (ECG). Those in whom AF is confirmed can be offered treatment to reduce their risk of having a stroke. In 2005 a Health Technology Assessment (HTA) concluded that opportunistic screening is the most cost-effective method to identify AF in a community population aged 65 years and over (Hobbs et al 2005). That HTA included a randomised controlled trial (RCT), but its scope was restricted by the funding body to the case identification component of screening, so the effects of treatment for screen-detected AF were not assessed.

The Condition

The condition should be an important health problem

2. AF is a major risk factor for stroke, leading to a fivefold increase in risk (Wolf et al 1991). The proportion of strokes associated with AF increases progressively with age, ranging from 7% in individuals aged 50-59 years to 36% in those aged 80-89 years (Wolf et al 1991, Arboix et al 2008). The prevalence of AF among people in the UK aged 65 and over is approximately 7%. A recent population-based study from Dublin found that the crude incidence rate of all AF-associated stroke is approximately 60 per 100,000 person years (Hannon et al 2010), which equates to about 35,000 strokes per annum in the UK. Another source states that AF accounts for about a sixth of all strokes (Raju and Hankey 2010), an estimate that equates to about 25,000 strokes per annum in the UK.

The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

3. A crucial question regarding the natural history of AF is whether screen-detected cases have the same risk of stroke (and hence the same potential to benefit from treatment) as those that are detected through routine clinical practice. Given the paucity of evidence relevant to this question, it was necessary to include studies which compare people with asymptomatic AF against those with symptomatic AF. This comparison is slightly different from that between screen-detected and routinely-detected AF, since it is likely that a small

proportion of screen-detected patients are symptomatic, and a minority of routinely-detected patients are asymptomatic.

4. The 2006 NICE Clinical Guideline on AF noted that many patients develop AF asymptomatically, and only present to medical care when complications such as stroke or heart failure occur. The literature review for the 2006 NICE guideline found no studies that have assessed whether asymptomatic AF *per se* is a potential risk factor for stroke. Nonetheless, the guideline development group agreed that asymptomatic AF should be treated no differently to symptomatic AF (National Collaborating Centre for Chronic Conditions 2006:96). The 2014 update of the NICE guideline states that its recommendations on anticoagulation apply to all patients with AF, irrespective of whether they were symptomatic (National Clinical Guideline Centre 2014). It does not cite any studies that have assessed whether asymptomatic AF *per se* is a potential risk factor for stroke, which suggests that the Guideline Development Group relied on consensus when making this statement.

5. The current review has found three publications relevant to this question. A trial by Mant et al (2007) found that, among people aged 75 years or over who had been randomized to either aspirin or warfarin, the risk of a major event (fatal or disabling stroke [ischaemic or haemorrhagic], intracranial haemorrhage, or clinically significant arterial embolism) was lower (annual risk 2.2% vs 3.1%) among patients who had been recruited through screening than among those that had been detected through routine clinical practice. However, this difference in risk of a major event was not statistically significant (19/290 vs. 53/683, chi-squared 0.28, 1df, p >0.5).

6. Healey et al (2012) found that, among patients with a pacemaker and hypertension, subclinical atrial tachyarrhythmias (detected by a pacemaker) increase the risk of stroke 2.5 times. This increase is only half the 5-fold increase in risk that is attributable to clinically diagnosed AF. The findings of this study may not be relevant to screen-detected AF, because the latter would be mainly subclinical persistent AF, not the subclinical paroxysmal AF that was picked up by the pacemakers in this study, but if the findings are relevant at all they indicate that the risk of stroke in subclinical AF might be only about half the risk of stroke in clinical AF. The authors noted that although the net benefit of antithrombotic treatment is well established in patients with clinical atrial fibrillation there may not be a similar benefit in patients with subclinical atrial tachyarrhythmias; they proposed that therefore a randomized trial of anticoagulant therapy in patients with subclinical atrial tachyarrhythmias is desirable.

7. Probably the most useful evidence comes from the AFFIRM study (Flaker et al 2005). Among patients with AF who were either >65years or, if <65 years, had at least 1 risk factor for stroke, over 5 years' follow-up there was a trend for better survival in asymptomatic patients (81% vs 77%, P = .058), and they were more likely to be free from disabling stroke or anoxic encephalopathy, major bleeding, and cardiac arrest (79% vs 67%, P = .024). The authors state that, after correction for baseline differences, mortality and major events were similar in the two groups (hazard ratio for death in symptomatic vs asymptomatic AF =

1.07, 95%CI 0.79-1.46; hazard ratio for major events 1.14, 95%CI 0.87-1.50). The 95% confidence intervals around these estimates include the possibility that asymptomatic AF carries only two-thirds of the mortality and major event risks of symptomatic AF. Furthermore, the authors did not take account of the greater number of patients with a history of stroke or transient ischaemic attack (TIA) among the group with asymptomatic AF (17% vs. 13%), and correction for this difference at baseline would further reduce the apparent risks associated with asymptomatic AF.

All the cost-effective primary prevention interventions should have been implemented as far as practicable

8. The known modifiable risk factors for AF are a history of myocardial infarction, angina, diabetes mellitus, hyperthyroidism, stroke or TIA (Hobbs et al 2005:5).However, robust evidence that managing these risk factors does indeed reduce the incidence of AF is limited. Retrospective analyses and reports from studies in which AF was a pre-specified secondary endpoint have shown a sustained reduction in new-onset AF with ACE inhibitors and angiotensin receptor blockers in patients with significant underlying heart disease (e.g. left ventricular dysfunction and hypertrophy), but there have been no formal RCTs to test this effect in the primary prevention setting (Savelieva et al 2011). A meta-analysis of RCTs found that the beneficial effect of statins on AF suggested by published shorter term studies is not supported by a comprehensive review of published and unpublished evidence from larger scale trials (Rahimi et al 2011).

9. All four UK countries have programmes in place to help prevent heart disease, stroke and diabetes mellitus and these may help to reduce the age-specific prevalence of AF, by preventing these modifiable risk factors for AF.

If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications

10. Not relevant to screening for AF.

The Test

There should be a simple, safe, precise and validated screening test and The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

11. The 2005 HTA concluded that active screening for AF detects additional cases over current practice, and that the preferred method of screening in patients aged 65 or over in primary care is opportunistic pulse taking, with follow-up electrocardiography if the pulse is irregular (Hobbs et al 2005:63). However, atrial flutter is also a risk factor for stroke and it may not be detected if irregular pulse is used as a screening mechanism (personal communication from Dr Ameet Bakhai).

12. The gold standard for diagnosis of AF is a 12-lead ECG read by at least one cardiologist. Against this gold standard, the best diagnostic performance in primary care was obtained by the combination of both GPs and computerised software reading 12-lead ECGs. The relevant test performance data for diagnosis of AF are as follows:

- Step 1 (practice nurse taking pulse): sensitivity 87% , specificity 81% (Hobbs et al 2005:45, Table 56)
- Step 2 (ECG for patients found to have an irregular pulse, read by both computerised software and GP): sensitivity 92%, specificity = 91% (Mant et al 2007)
- Steps 1 and 2 combined: sensitivity = 80% (= 87% X 92%), specificity = 91%

13. The 2005 HTA report concluded that 'the performance of GPs and practice nurses in terms of ECG interpretation was disappointing; however, the computerised software performed well and represents a realistic alternative to expert interpretation' (Hobbs et al 2005:63). However, in a later journal article the authors drew a somewhat different conclusion from the same data (Mant et al 2007):

> Computer software performed much better, but still had an error rate sufficiently high to mean that decisions on treatment cannot be based on diagnosis by computer alone, even when combined with interpretation by a general practitioner. Therefore, strategies to identify AF in the community, whether through population screening or for diagnosis of patients with symptoms, need to take into account how and by whom the electrocardiogram will be interpreted.

14. Lewis et al (2011) report the performance, against 12-lead ECG as gold standard, of screening using computerized analysis of 30 seconds of pulse waveform pattern obtained using a finger-probe instrument (as used in pulse oximetry). In a post hoc analysis of data from 594 hospital-based patients, the authors were able to adjust the test cut-off to obtain 100% sensitivity with 92% specificity. The performance of this method, and the proposed cut-off, needs to be validated in an independent, preferably community-based, population.

15. Hospital based studies assessing the performance of using a modified blood pressure monitor, similar to those used by patients to monitor their blood pressure at home, suggest that a sensitivity of greater than 90% could be achieved while maintaining reasonable specificity (84%–92%) (Harris et al 2012).

16. Finger probes and modified blood pressure monitors might reduce the number of ECGs that need to be read to confirm or exclude a diagnosis of AF, but a screening programme would still generate substantial additional numbers of ECGs. Strategies suggested by Mant et al (2007) for ensuring that ECGs could be read in sufficient quality and quantity were training and accreditation of GPs, and electronic telemedicine transfer of ECGs for reading by specialists. However, the question of how the large number of ECGs that would be generated by a screening programme for AF would be read to an acceptable level of sensitivity and specificity does not yet seem to have been resolved.

The test should be acceptable to the population

17. The HTA test uptake data are reassuring on this point. Among opportunistically screened patients who were found to have an irregular pulse, 73% had an ECG (Hobbs et al 2005:39,Table 40). In a post-screening questionnaire the HTA found that 94% reported that the letter / information sheet they received had explained things properly, and only 3.7% found that the screening was not convenient (Hobbs et al 2005:49).

There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

18. This is covered by the 2014 update of NICE Clinical Guideline 36 (National Clinical Guideline Centre 2014).

If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

19. Not relevant to screening for AF.

The Treatment

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

20. The potential advantage of early detection and treatment of AF is that it may prevent a stroke which, in the absence of screening, might be the sentinel event through which AF is first diagnosed. The disadvantage of treatment is that it increases the risk of major haemorrhage.

Vitamin K antagonists (e.g. warfarin) and aspirin

21. The anti-thrombotic treatments for AF recommended by the 2006 NICE Clinical Guideline were warfarin and aspirin, with warfarin recommended for those at higher risk of stroke (National Collaborating Centre for Chronic Conditions 2006). The 2014 update of this guideline recommends that aspirin monotherapy should not be offered solely for stroke prevention to people with atrial fibrillation (National Clinical Guideline Centre 2014).

22. Unfortunately, warfarin has a narrow therapeutic window, interacts substantially with other drugs and food, and requires coagulation monitoring. Among adults with nonvalvular atrial fibrillation who received care within Kaiser Permanente of Northern California, more than 1 in 4 patients newly starting warfarin for atrial fibrillation discontinued therapy in the first year (defined as ≥180 consecutive days off warfarin) despite a low overall hemorrhage rate (Fang et al 2011).

23. The 2005 HTA report on screening for AF assumed that treatment would be beneficial in screen-detected AF in the elderly: [screening for AF] 'fulfils many of the Wilson–Jungner criteria for a screening programme ... the risk of serious sequelae such as stroke can be dramatically reduced by treatment' (Hobbs et al 2005:2). However, the RCT evidence on the benefits of treatment is derived from patients whose AF was detected through routine clinical care, rather than through screening. As previously pointed out, it is uncertain whether screen-detected AF carries the same risk of stroke (and hence the same potential to benefit from treatment) as AF that is detected through routine clinical practice.

24. Proof that anti-thrombotic treatment produces net benefits for patients with screen-detected AF (i.e. that the absolute reduction in risk of stroke exceeds the absolute increase in risk of major extra-cranial haemorrhage or other serious adverse outcome) could be provided by a placebo-controlled RCT among this patient group. Unfortunately, no such trial has been performed. The closest approximation appears to be the trial by Mant et al (2007), in which 290 people aged 75 years or over with screen-detected AF were randomized to either aspirin or warfarin. Since warfarin is much more effective than aspirin in preventing stroke among routinely-detected cases of AF, demonstration of the same result among screen-detected cases of AF would strongly suggest that, compared with no treatment, warfarin delivers net benefits for screen-detected cases of AF.

25. The results of the RCT did favour warfarin over aspirin, but the confidence intervals were too wide to be certain of this conclusion (relative risk of a primary event 0.85, 95% CI 0.31–2.33). The same trial demonstrated the superiority of warfarin over aspirin for patients whose AF was already known from practice registers i.e. cases detected through routine clinical care (relative risk of a primary event 0.38, 95% CI 0.20–0.71). The authors also noted that there was no evidence of an interaction between the effectiveness of warfarin and the way in which AF had been detected. However, this falls short of saying that we can be confident that the effectiveness of warfarin is the same in both routinely-detected and screen-detected AF. It has therefore not yet been demonstrated beyond doubt that antithrombotic treatment produces net benefits for patients with screen-detected AF.

New oral anticoagulants

26. NICE has published technology appraisals recommending apixaban, dabigatran exilate and rivaroxaban as options for preventing stroke and systemic embolism within their marketing authorisations, that is, in people with nonvalvular atrial fibrillation with 1 or more specified risk factors (NICE 2012 and 2013). The 2014 update of the NICE AF guideline states that anticoagulation may be with apixaban, dabigatran etexilate, rivaroxaban or a vitamin K antagonist. It recommends that doctors should discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences (National Clinical Guideline Centre 2014).

27. Given the known substantial difficulties with warfarin, and the importance of achieving a high level of confidence that the benefit of a screening programme will outweigh the physical and psychological harm, it seems likely that many patients with screen-detected AF would need to be offered treatment with one of the new oral anticoagulants rather than warfarin.

There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

28. Tools are available for assessing individuals' risk of stroke and their risk of bleeding. The performance of these tools is commonly summarised by using the c-statistic, or area-under-the-curve. A c-statistic of 1.0 indicates perfect ability to predict the risk of stroke or bleeding, and a score of 0.5 indicates no predictive value. Before giving brief details of some current tools, the following narrative assessment given by Fraenkel and Fried (2010) helps to set the scene:

> Despite the wealth of studies in nonvalvular atrial fibrillation, many assumptions are necessary to calculate patient-specific outcomes, and these assumptions may lead to substantial overestimation or underestimation of benefits and harms. Improving care for patients with co-morbidities will require substantive increases in the efforts and resources allocated to the collection and dissemination of outcome data for patients with varying co-morbidities.

Assessing the risk of stroke

29. At least 19 different schemes have been developed for assessing the risk of stroke in patients with AF, though none of them has been evaluated in patients with screen-detected AF. The most commonly used risk stratification scheme is $CHADS_2$. CHA_2DS_2-VASc was developed to complement $CHADS_2$ by considering additional thromboembolic risk modifiers. Large population-based studies in the UK (Van Staa et al 2011) and Denmark (Olesen, Lip, Hansen et al 2011) have found that CHA_2DS_2-VASc is more valid for stroke prediction in patients categorised as being at low and intermediate risk by the $CHADS_2$ scheme. This is clinically important, as many of the patients at low risk according to $CHADS_2$ are not at truly low risk and treatment guidelines are not conclusive for those at intermediate risk. The UK and Danish studies reported c-statistics for CHA_2DS_2-VASc of 0.67 and 0.78 respectively, indicating a performance for stroke prediction that is roughly half-way between 'no predictive value' and 'perfect'. A small (665 patients) community-based study of patients aged 75 or over with atrial fibrillation found that current risk stratification schemes in older people with atrial fibrillation have only limited ability to predict the risk of stroke, and recommended classifying all patients over 75 as 'high risk' until better tools are available (Hobbs et al 2011). The 2014 update of the NICE AF guideline includes the following recommendation (National Clinical Guideline Centre 2014):

> 'Use the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following:
> - symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation
> - atrial flutter
> - a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm.

Assessing the risk of bleeding

30. This review identified several studies that have assessed the performance of different risk scores for predicting the risk of bleeding in patients with AF who are taking warfarin. Studies have reported a c-statistic of approximately 0.7 for the ATRIA score (Fang 2011) and a range of approximately 0.7 – 0.8 for the HAS-BLED score (Pisters et al 2010; Lip, Frison et al 2011; Olesen, Lip, Hansen, Lindhardsen et al 2011). A systematic review of studies of the association between $CHADS_2$ covariates and risk of bleeding in patients receiving warfarin found that the associations between $CHADS_2$ covariates and increased bleeding risk were weak, with the exception of age. The authors concluded that, given the known association of the $CHADS_2$ score and stroke risk, the decision to prescribe warfarin should be driven more by patients' risk of stroke than by the risk of bleeding (Chen et al 2011).

31. The 2014 update of the NICE AF guideline includes the following recommendations (National Clinical Guideline Centre 2014):

> 'Use the HAS-BLED score to assess the risk of bleeding in people who are starting or have started anticoagulation. Offer modification and monitoring of the following risk factors:
> - uncontrolled hypertension

- poor control of international normalised ratio (INR) ('labile INRs')
- concurrent medication, for example concomitant use of aspirin or a non-steroidal anti-inflammatory drug (NSAID)
- harmful alcohol consumption.

When discussing the benefits and risks of anticoagulation, explain to the person that:

- for most people the benefit of anticoagulation outweighs the bleeding risk
- for people with an increased risk of bleeding the benefit of anticoagulation may not always outweigh the bleeding risk, and careful monitoring of bleeding risk is important.

Do not withhold anticoagulation solely because the person is at risk of having a fall.'

Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

32. Numerous studies have demonstrated that, among people with AF, compliance with currently recommended anti-thrombotic treatments is poor. Many people who, according to the 2006 NICE guideline, should be on anticoagulants are not; many people who should not be on anticoagulants are on anticoagulants; and among those who are taking warfarin the level of anticoagulation is often too high or too low. A few recent examples from the UK are described below.

Are the right patients on anticoagulants?

33. In a study of primary care in England during the period 2009-2012, Cowan et al (2012) found that 34% of 132,099 patients with a $CHADS_2$ score ≥2, were not on anticoagulant therapy and were without a recorded contraindication or recorded refusal; and 34% of 37,771 patients with a $CHADS_2$ score=0 were prescribed anticoagulant therapy. The effect of using CHA_2DS_2-VASc rather than $CHADS_2$ to estimate stroke risk was shown by Holt et al. (2012) in a UK study of 59,804 primary care patients with AF. They found that the proportion of people with AF and at high risk of stroke who were receiving anticoagulants in 2010 was 53.0% (with stroke risk defined according to the $CHADS_2$ ≥2 threshold) or 50.7% (with stroke risk defined according to the CHA_2DS_2-VASc ≥2 threshold). Higher than expected usage of anticoagulant therapy was found in the low-risk groups: 32.1% of people with $CHADS_2$ = 0 and 23.0% with CHA_2DS_2-VASc = 0.From these data there appears to be substantial room for improvement in which patients with AF are, and are not, prescribed anticoagulants in UK primary care.

34. NHS Improvement has made available a query and risk stratification tool (GRASP-AF) that helps GPs to identify patients with AF who are not on warfarin but might benefit from it. It does not identify patients with AF who are on warfarin but should not be on it (http://www.improvement.nhs.uk/graspaf/).

35. National QOF data for 2012-13 confirm that a large proportion (35%) of patients with clinically-diagnosed AF who should be taking an anticoagulant (because they have a $CHADS_2$ score ≥ 2 and are not reported as having a contraindication to taking an anticoagulant) are not taking an anticoagulant. The extent to which the introduction of dabigatran exilate, apixaban and rivaroxaban as alternatives to warfarin will lead to better management of patients with AF remains to be seen.

36. A systematic review (Pugh et al 2011) has identified reasons why physicians are reticent to recommend warfarin for elderly patients with AF, despite evidence of increased benefit in these patients compared with younger patients. Risk of falls and previous bleeding were shown to be disproportionate barriers to warfarin prescription. The authors recommended further studies to determine how best to overcome these perceived barriers to appropriate anticoagulation.

Is the INR in the recommended range?

37. It is difficult for people who are taking warfarin to maintain their level of anticoagulation within the recommended range (2.0 to 3.0) of the international normalized ratio (INR). The anticoagulant effect of warfarin is influenced by diet and other medicines, and many people forget to take their pills: in a US study of 136 participants observed for a mean of 32 weeks, 36% missed more than 20% of their doses (Kimmel et al 2007). A systematic review found that the average time that warfarinized patients spend within the recommended INR range was 59% for those with infrequent monitoring and 64% for those with frequent monitoring (Dolan et al 2008). The authors concluded that it may therefore be inappropriate to extrapolate data on efficacy and safety of anticoagulants from RCTs to 'real life' situations.

38. This concern is borne out by a post hoc analysis of data from RCTs of warfarin therapy, and several observational studies in the UK. Among 3,587 patients with AF who had been randomized to receive warfarin, those with good control (defined as INR of 2.0-3.0 for >75% of the time) had outcomes that were roughly twice as favourable as those with poor control (defined as INR of 2.0-3.0 for <60% of the time) on various measures: annual mortality (1.69% vs. 4.20%), risk of stroke or systemic embolism event (1.07% vs. 2.10%), risk of major bleeding (1.58% vs. 3.85%), and risk of myocardial infarction (0.62% vs. 1.38%) (White et al 2007). A model based on data from 3,371 AF patients randomized to receive an oral anticoagulant predicted that they would need to be within the recommended INR range for at least 58% of the time to be confident that they were receiving any net benefit (Connolly et al 2008).

39. An observational UK study of 51,000 patients found that, although warfarin reduces the rate of stroke in chronic AF patients in the general clinical practice setting, the risk reduction is lower than that reported in clinical trials. When current users of warfarin were compared with former users, the risk of stroke in current users was reduced by only 38%, not the 60% reported from RCTs (Rietbrock et al 2009). The same group found that patients who spent at least 70% of time within the therapeutic range had a 79% reduced risk of stroke

compared to patients with ≤30% of time in range (Gallagher et al 2011). A Welsh record-linkage study found that people with AF who managed to maintain a stable INR (defined as six months within the target INR range of 2.0-3.0) did much better than those with an unstable INR in terms of both thromboembolic events (0.8% vs. 2.3% per patient year) and bleeds recorded on inpatient diagnoses (0.4% vs. 1.2% per patient year) (Currie et al 2005). Stroke risk was only reduced in AF patients at moderate or high risk who were eligible for and treated with warfarin, and whose INR was within the therapeutic range more than 70% of the time; overall mortality was only reduced in those whose INR was within the therapeutic range more than 40% of the time (Morgan et al 2009). The authors concluded that poorly controlled warfarin therapy is potentially harmful and proposed that if good control cannot be achieved, the therapy should be stopped.

The Screening Programme

There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity

40. There have been no randomised controlled trials of screening for AF that have assessed its impact on mortality or morbidity.

There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

41. In March 2012 the Royal College of Physicians of Edinburgh published a consensus statement that includes the following recommendation in favour of screening: 'Screening for AF in people of 65 or older satisfies the UK NSC criteria for a screening programme and such a national screening programme should be undertaken in the UK.' The same statement also points out that 'the use of oral anticoagulants (OACs) is inadequate. There is an urgent need to ... encourage better uptake and adherence to OACs'. Without better uptake and adherence to OACs it is hard to see how screening for AF satisfies the UK NSC criteria for a screening programme, since one of the NSC criteria is that 'clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme'.

42. The limited evidence available suggests that patients and health professionals differ in the way they evaluate the benefits and risks of anticoagulation. A systematic review found that treatment recommendations from clinical practice guidelines often differ from patient preferences, with substantial heterogeneity in their individual preferences. In 6 of 8 studies, patient preferences indicated that fewer patients would take warfarin compared to the recommendations of the guidelines (Man-Son-Hing et al 2005).

43. In a small RCT in two research clinics in Northeast England, patients with AF aged over 60 were much less likely to start warfarin if they used a computerised decision aid in a shared decision-making consultation than if they were advised by doctors using paper guidelines (4/16 vs. 15/16, RR 0.27, 95% CI 0.11 to 0.63) (Thomson et al 2007).

The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

44. It is likely, but not proven, that a national screening programme for atrial fibrillation in people aged 65 and over would produce more benefit than harm, provided that the NHS

can greatly improve its performance in providing safe anticoagulant therapy to appropriate patients.

The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money)

45. The 2005 HTA modelled the cost-effectiveness of screening for AF and concluded that there was a probability of approximately 60% that annual opportunistic screening from the age of 65 years was cost-effective in both men and women (Hobbs et al 2005:iv). However, the model assumed that anti-thrombotic treatments have the same effects in screen-detected AF as in routinely-detected AF, and the report does not describe whether the model reflected real-world (i.e. low) compliance with guideline-recommended anti-thrombotic treatments.

46. The 2014 update of the NICE AF guideline used a more sophisticated health economic model than previous publications. Probabilistic base case analysis showed greatest net benefit is most likely if no drug is given unless the patient has CHA_2DS_2VASc score ≥ 2 and HAS-BLED score =0. In the deterministic base case analysis, overall a 'do nothing' approach was found marginally optimal in comparison to other strategies. The authors noted that there are currently few studies which validate commonly used bleeding and stroke risk scoring systems, meaning the uncertainty in the scoring system's predictive power cannot be easily evaluated or incorporated into economic models (National Clinical Guideline Centre 2014, Appendix L).

47. A formal assessment of the cost-effectiveness of a screening programme is required. It should include the costs of detecting cases and take into account the possibility that patients with screen-detected AF have a lower risk of stroke than patients with clinically-diagnosed AF.

There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

48. Consideration of this potential screening programme is at an early stage, so such a plan and standards do not yet exist. However, the Quality and Outcomes Framework (QOF) for 2012-13 included the following relevant quality indicators:

- The practice can produce a register of patients with atrial fibrillation
- The percentage of patients with Atrial Fibrillation in whom stroke risk has been assessed using the $CHADS_2$ risk stratification scoring system in the preceding 15 months
- In those patients with Atrial Fibrillation in whom there is a record of a $CHADS_2$ score of >1, the percentage of patients who are receiving anticoagulants.

49. A consensus statement from the Royal College of Physicians of Edinburgh recommends that all providers of anticoagulation services should provide annual data of TTR (time in therapeutic range) as a means of quality improvement (RCPE 2012).

Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

50. It is not yet clear which type(s) of clinical staff should read the ECGs that would be generated by a screening programme, hence it is not possible to assess the adequacy of staffing for this function.

51. Data from the 2005 HTA suggests that screening would not massively increase the workload involved in monitoring anticoagulation. In the opportunistic screening arm of the HTA trial there were 340 patients with AF at baseline, and 75 new cases were detected during the next 12 months, of which 28 were attributable to screening (Hobbs et al 2005:29,51). This indicates that screening might result in an increase in the total number of diagnosed cases of AF of about 8%. Only a proportion of these would be at sufficiently high risk of stroke to be eligible for anticoagulation, and many of them might be treated with one of the new oral anticoagulants rather than warfarin and therefore not need regular monitoring by anticoagulation services.

All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available

52. The main purpose of screening for AF is to prevent stroke. In addition to AF, other well-documented and potentially modifiable risk factors for stroke include hypertension, exposure to cigarette smoke, diabetes, dyslipidaemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity, and obesity - especially truncal obesity (Goldstein et al 2006). It is not yet clear whether screening for AF would be more cost-effective than efforts to improve the management of other high-prevalence risk factors for stroke such as hypertension, diabetes or dyslipidaemia.

53. Given the known poor compliance among people with routinely-detected AF with recommended treatments, better treatment for this group of people might prove more cost-effective than introducing a screening programme. Better treatment might involve strategies to improve the quality of anticoagulation in those who are currently recommended to receive warfarin treatment, or introducing one of the new oral therapies that do not require coagulation monitoring.

54. A Cochrane review (Garcia-Alamino et al 2010) found that self-monitoring or self-management of oral anticoagulant therapy compared to standard monitoring reduced both thromboembolic events (RR 0.50, 95% CI 0.36 to 0.69) and all-cause mortality (RR 0.64, 95% CI 0.46 to 0.89). A recent RCT (Matchar et al 2011) found that, compared to monthly high-quality testing in a clinic, weekly self-testing at home achieved a small (3.8%) but significant improvement in the percentage of time during which the INR was within the target range, and a non-significant increase in the time to a first major event (stroke, major bleeding episode, or death) (hazard ratio, 0.88; 95% confidence interval, 0.75 to 1.04). However, a previous HTA (Connock et al 2007) found that only 14% of eligible patients would conduct long-term self-monitoring, and the estimated probability that patient self-monitoring is cost-effective (up to £30,000 / QALY) was only 44% over a 10-year period.

55. Other potential improvements that are associated with better outcomes for people with routinely-detected AF include a specialized anticoagulant management service, computerized decision support systems and increased test frequency. Dosing algorithms that incorporate both clinical and genetic factors may increase the capacity to improve dosing of warfarin (Ryan et al 2008).

Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

56. The NHS Choices website includes a series of pages about AF (http://www.nhs.uk/Conditions/Atrial-fibrillation/Pages/Introduction.aspx). These reflect the professional perspective contained in the relevant NICE guideline (National Collaborating Centre for Chronic Conditions 2006). However, it is important to bear in mind the (limited) evidence already cited (Man-Son-Hing et al 2005, Thomson et al 2007) that patients may evaluate the benefits and risks of warfarin treatment very differently from health professionals.

Public pressure for widening the eligibility criteria, for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

57. Given the strongly age-related prevalence of AF, and the risks of treatment, it seems unlikely there would be public pressure to expand the programme beyond what is currently being considered.

Implications for policy

It is likely, but not proven, that a national screening programme for atrial fibrillation in people aged 65 and over would produce more benefit than harm at population level but it is uncertain whether such a programme would be cost-effective. Current NHS management of AF that is detected through routine clinical practice is known to be frequently poor, both because patients who should receive anticoagulants do not receive anticoagulants, and because treatment with warfarin is often problematic. Before introducing a screening programme, the NHS should first demonstrate that it is managing AF much better than it has done to date, because it would be unethical to introduce a screening programme without being confident that screen-detected patients would be well managed. Points of note regarding this are:

- National QOF data for 2012-13 show that 35% of patients with AF who should receive warfarin do not receive warfarin. A screening programme that failed to offer effective treatment to such a large proportion of screen-positive patients could not be justified. The quality of anticoagulation in patients who are treated with warfarin is not routinely reported.
- The introduction of the new oral anticoagulants could lead to better NHS management of patients with AF, but this has yet to be demonstrated in practice. The role of these newer drugs in a potential screening programme should be clarified before a decision is taken on whether to initiate a national screening programme.

Other factors that should be taken into consideration before introducing a national screening programme for atrial fibrillation in people aged 65 years and over include:

- It is uncertain whether screen-detected AF carries the same risk of stroke as AF that is detected through routine clinical practice. The best available evidence (Flaker et al 2005) suggests that people with asymptomatic AF have similar risks of death and other major events to people with symptomatic AF, but the 95% confidence intervals around these estimates include the possibility that asymptomatic AF carries only two-thirds of the risk of symptomatic AF.
- Direct RCT evidence that antithrombotic treatment produces net benefits for patients with screen-detected AF is limited to one study that compared warfarin with aspirin (Mant et al 2007). The results of this RCT did favour warfarin, but the confidence intervals were too wide to be certain of this conclusion (relative risk of a primary event 0.85, 95% confidence interval 0.31–2.33).
- Given the large proportion of patients with AF who do not take oral anticoagulants in keeping with professional guidelines, and the limited evidence indicating that well-informed patients are less keen to take oral anticoagulants than professional guidelines recommend, good quality patient decision aids need to be developed to ensure that patients are equipped to make decisions that reflect individual values as well as evidence of benefits and harm.

- A formal assessment of the cost-effectiveness of a screening programme is required. It should include the costs of detecting cases and include a sensitivity analysis that reflects the possibility that patients with screen-detected AF have a lower risk of stroke than patients with clinically-diagnosed AF.

- There is a lack of clarity about which type(s) of clinical staff should read the ECGs that would be generated by a screening programme, and hence a lack of clarity about whether sufficient staff are in place.

Implications for research

- The optimal interval between screening rounds needs to be identified, perhaps through economic modelling of the differing clinical yields (Fitzmaurice et al 2007).

Appendix 1

Knowledge update on screening for atrial fibrillation
Paula Coles, Information Scientist
July 2010

BACKGROUND: A literature search was performed to find citations on screening for atrial fibrillation, for the prevention of stroke in people aged 65 and over. The current policy is based on the following Health Technology Assessment:

Hobbs FDR, Fitzmaurice DA, Jowett S, Mant J, Murray E, Bryan S, *et al*. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine = practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technology Assessment* 2005; 9(40) Full text: http://www.hta.ac.uk/fullmono/mon940.pdf [accessed 28 June 2010]

SOURCES SEARCHED: Medline (OvidSP), Embase, PsychINFO, Cinahl, Web of Knowledge and the Cochrane Library.

DATES OF SEARCH: As the evidence the current policy was based on was published in 2005, the searches were performed from January 2005 to June 2010.

SEARCH STRATEGY: Medline OvidSP

1. Atrial Fibrillation/ (25323)
2. (atrial fibrillation or AF).tw. (33779)
3. 1 or 2 (40905)
4. Mass Screening/ (67624)
5. screen$3.tw. (334247)
6. detect$3.tw. (1159968)
7. (test or tests or testing).tw. (1151668)
8. 4 or 5 or 6 or 7 (2363026)
9. Echocardiography/ (56572)
10. (echocardiogra$ or ECG).tw. (118992)
11. Pulse/ (15644)
12. pulse.tw. (94128)
13. "Sensitivity and Specificity"/ (224359)
14. (sensitiv$ and specific$).tw. (225858)
15. "Predictive Value of Tests"/ (102706)
16. (positive predictive value$ or negative predictive value$).tw. (22439)
17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (684503)
18. 8 and 17 (267874)
19. Anticoagulants/ (42601)
20. Warfarin/ (11519)
21. Platelet Aggregation Inhibitors/ (20337)
22. Aspirin/ (33354)
23. (warfarin or aspirin).tw. (40301)
24. (anticoagula$ or anti-coagula$).tw. (50089)
25. thromboprophylaxis.tw. (1629)
26. (anti-thrombotic or antithrombotic).tw. (10202)
27. exp "Patient Acceptance of Health Care"/ (124675)

28. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (257860)
29. quality-adjusted life years/ (4402)
30. QALY$.tw. (3036)
31. "Quality of Life"/ (83379)
32. QOL.tw. (11549)
33. Stroke/ (36396)
34. stroke.tw. (102233)
35. death$.tw. (410476)
36. cerebrovascular accident$.tw. (4310)
37. morbid$.tw. (193442)
38. "Outcome Assessment (Health Care)"/ (36382)
39. Fatal Outcome/ (39613)
40. Treatment Outcome/ (427673)
41. outcome$.tw. (600073)
42. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 (1539269)
43. 28 and 42 (69629)
44. 8 and 42 (251448)
45. 18 or 43 or 44 (543989)
46. 3 and 45 (5997)
47. limit 46 to yr="2005 -Current"
48. limit 47 to ("all aged (65 and over)" or "aged (80 and over)")

Similar searches were also carried out in Embase, PsychINFO, Cinahl, Web of Knowledge and the Cochrane Library.

All searches carried out on 28 June 2010

The above search strategies retrieved 6145 references in total. After duplicate references were removed a total of 3745 potentially relevant references were left. The title and abstracts of the remaining citations were scanned for relevance to screening for atrial fibrillation, focussing on the NSC criteria, and particularly looking for:

- People aged 65 and over

The condition
- The natural history of screen-detected vs. incident atrial fibrillation

The test
- The role of computerised decision support software, including cost and acceptability
- The performance of GPs and practice nurses in interpreting ECGs

The treatment
- Treatment in screen-detected or incident atrial fibrillation
- Evaluations of thromboprophylactic treatments in patients with atrial fibrillation

The screening programme
- Screening for atrial fibrillation
- Routine detection of atrial fibrillation

383 references were deemed to be relevant and are classified in to the categories below according to the NSC criteria. There will inevitably be some overlap between categories.

Systematic reviews and meta-analyses • Outcomes (3) • Treatments (16) • Adverse events (2) • Management (3) • Detection (1) • Costs (1)	**26**
Guidelines	**3**
The condition • Incidence/prevalence (6) • Risk of stroke (19) • Risk of stroke and age (3) • Risk of stroke and gender (2) • Stroke outcomes (13) • Mortality (7) • Progression of paroxysmal AF to permanent AF (4) • Gender differences (2) • Ethnicity (3) • Cognitive decline (1) • Quality of life (11) • Economic burden (6)	**77**
The test	**4**
The treatment (see appendix for details)	**268**
The screening programme	**5**
Total	**383**

References

Albers GW. Stroke: more protection for patients with atrial fibrillation [Review]. *Lancet neurol* 2010;9(1):2-4.

Arboix A, Cendros V, Besa M, *et al.* Trends in risk factor, stroke subtypes, and outcome: nineteen-year data from the Sagrat Cor Hospital of the Barcelona Stroke Registry. *Cerebrovasc Dis* 2008; 26:509–516.

Christie B. People over 65 should be screened for atrial fibrillation, say stroke specialists. BMJ 2012;344:1

Connock M, Stevens C, Fry-Smith A, *et al*. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. *Health Technology Assessment* 2007;11(38)

Connolly SJ, Pogue J, Eikelboom J, *et al*. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008(20):2029-37.

Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine 2*009;361(12):1139-51.

Cowan C, Healicon R, Robson I, Long WR, Barrett J, Fay M, Tyndall K, Gale CP. The use of anticoagulants in the management of atrial fibrillation among general practices in England. *Heart Published Online First*: doi:10.1136/heartjnl-2012-303472

Currie CJ, McEwan P, Emmas C, *et al.* Anticoagulation in patients with non-valvular atrial fibrillation: an evaluation of stability and early factors that predict longer-term stability on warfarin in a large UK population. *Current Medical Research and Opinion* 2005;21(12):1905-13.

Dolan G, Smith LA, Collins S, *et al*. Effect of setting, monitoring intensity and patient experience on anticoagulation control: a systematic review and meta-analysis of the literature. *Current Medical Research and Opinion* 2008;24(5):1459-72.

Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the Tipping Point The Decision to Anticoagulate Patients With Atrial Fibrillation. *Circulation-Cardiovascular Quality and Outcomes* 2011; 4(1):14-21

Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N et al. Warfarin discontinuation after starting warfarin for atrial fibrillation. Circulation Cardiovascular Quality & Outcomes 2010; 3(6):624-631.

Fitzmaurice DA, Hobbs FDR, Jowett S, *et al*. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. *British Medical Journal* 2007;335(7616):383-86.

Flaker GC, Belew K, Beckman K, *et al*. Asymptomatic atrial fibrillation: demographic features and prognostic information from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *American Heart Journal* 2005;149(4):657-63.

Fraenkel L, Fried TR. Individualized Medical Decision Making Necessary, Achievable, but Not Yet Attainable. Archives of Internal Medicine 2010; 170(6):566-569.

Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thrombosis and Haemostasis 2011; 106 (5):968-977.

Garcia-Alamino JM, Ward AM, Alonso-Coello P, *et al*. Self-monitoring and self-management of oral anticoagulation. *Cochrane Database of Systematic Reviews* 2010(4).

Garcia D, Libby E, Crowther MA. The new oral anticoagulants [Review]. *Blood* 2010;115(1):15-20.

Goldstein LB, Adams R, Alberts MJ, et al; Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council;

Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2006 Jun 20;113(24):e873-923.

Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine 2011; 365(11):981-992

Hannon N, Sheehan O, Kelly L, *et al*. Stroke associated with atrial fibrillation--incidence and early outcomes in the north Dublin population stroke study. *Cerebrovascular Diseases* 2010;29(1):43-9.

Harris K, Edwards D, Mant J. How can we best detect atrial fibrillation? Paper prepared for RCP UK Conference on Atrial Fibrillation, March 2012.

Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine* 2007;146(12):857-67.

Healey J, Connolly S, Gold M et al. Subclinical atrial fibrillation and the risk of stroke *N Engl J Med* 2012;366:120-9

Hobbs FDR, Fitzmaurice DA, Jowett S, Mant J, Murray E, Bryan S, *et al*. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technology Assessment* 2005; 9(40)

Hobbs FDR, Roalfe AK, Lip GYH, Fletcher K, Fitzmaurice DA, Mant J et al. Performance of stroke risk scores in older people with atrial fibrillation not taking warfarin: comparative cohort study from BAFTA trial. BMJ 2011; 342:d3653.

Holt TA, Hunter TD, Gunnarsson C, Khan N, Cload P and Lip GYH. Risk of stroke and oral anticoagulant use in atrial fibrillation: a cross-sectional survey. British Journal of General Practice 2012; 62: 710-7.

Kimmel SE, Chen Z, Price M, *et al*. The influence of patient adherence on anticoagulation control with warfarin: Results from the international normalized ratio adherence and genetics (INRANGE) study. *Archives of Internal Medicine* 2007;167(3):229-35.

Lewis M, Parker D, Weston C, Bowes M. Screening for atrial fibrillation: sensitivity and specificity of a new methodology. British Journal of General Practice 2011; 61(582):38-39.

Lip GYH. OPINION The role of aspirin for stroke prevention in atrial fibrillation. Nature Reviews Cardiology 2011; 8(10):602-606

Lip GYH, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E et al. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. Europace 2011; 13(5):723-746.

Lip GYH, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. Journal of the American College of Cardiology 2011; 57(2):173-180.

Man-Son-Hing M, Gage BF, Montgomery AA, *et al*. Preference-based antithrombotic therapy in atrial fibrillation: Implications for clinical decision making. *Medical Decision Making* 2005;25(5):548-59.

Mant J, Hobbs R, Fitzmaurice D, *et al*. BAFTA: a randomised controlled trial of warfarin versus aspirin for stroke prevention in atrial fibrillation in a primary care population aged over 75. *Cerebrovascular Diseases* 2007(Suppl 2):10.

Mant J, Fitzmaurice DA, Hobbs FDR, et al. Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and interpretative diagnostic software: analysis of data from screening for atrial fibrillation in the elderly (SAFE) trial. *BMJ* 2007;335(7616):380.

Matchar DB, Jacobson A, Dolor R, Edson R, Uyeda L, Phibbs CS et al. Effect of home testing of international normalized ratio on clinical events. *New England Journal of Medicin*e 2010; 363(17):1608-1620.

Morgan CL, McEwan P, Tukiendorf A, *et al.* Warfarin treatment in patients with atrial fibrillation: Observing outcomes associated with varying levels of INR control. *Thrombosis research* 2009;124(1):37-41.

National Clinical Guideline Centre. *Atrial fibrillation: the management of atrial fibrillation*. 2014.

National Collaborating Centre for Chronic Conditions. *Atrial Fibrillation: National clinical guidance for management in primary and secondary care. CG36 Atrial fibrillation: full NICE guideline 2006.*

National Institute for Health and Clinical Excellence. *Technology appraisal guidance 249: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation.* March 2012.

National Institute for Health and Clinical Excellence. *Technology appraisal guidance 256: Rivarox*aban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. May 2012.

National Institute for Health and Clinical Excellence. *Technology appraisal guidance 275: Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation*. February 2013.

Olesen JB, Lip GYH, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study. Thrombosis and Haemostasis 2011; 106(4):739-749.

Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011; 342.

Olesen JB, Lip GYH, Hansen PR, Lindhardsen J, Ahlehoff O, Andersson C et al. Bleeding risk in 'real world' patients with atrial fibrillation: comparison of two established bleeding prediction schemes in a nationwide cohort. Journal of Thrombosis and Haemostasis 2011; 9(8):1460-1467.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine 2011; 365(10):883-891

Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138(5):1093-1100.

Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. Age Ageing 2011; 40: 675–83.

Rahimi K, Martin J, Emberson J, McGale P, Majoni W, Merhi A et al. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. BMJ 2011; 342 :d1250 doi:10.1136/bmj.d1250.

Raju NC, Hankey GJ. *Dabigatran etexilate in people with atrial fibrillation*. BMJ 2010;341:682-3.

Rietbrock S, Plumb JM, Gallagher AM, *et al*. How effective are dose-adjusted warfarin and aspirin for the prevention of stroke in patients with chronic atrial fibrillation?: An analysis of the UK general practice research database. *Thrombosis and haemostasis* 2009;101(3):527-34.

Royal College of Physicians of Edinburgh. UK Consensus Conference on “Approaching the comprehensive management of Atrial Fibrillation: Evolution or revolution?” 1 & 2 March 2012

Ryan F, Byrne S, O'Shea S. Managing oral anticoagulation therapy: improving clinical outcomes. A review. *Journal of Clinical Pharmacy and Therapeutics* 2008;33(6):581-90.

Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part I: primary prevention. Europace 2011; 13(3):308-328.

The Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 84, 527–539 (1991).

Thomson RG, Eccles MP, Steen IN, *et al*. A patient decision aid to support shared decisionmaking on anti-thrombotic treatment of patients with atrial fibrillation: Randomised controlled trial. *Quality and Safety in Health Care* 2007;16(3):216-23.

van Staa TP, Setakis E, di Tanna GL, Lane DA, Lip GYH. A comparison of risk stratification schemes for stroke in 79 884 atrial fibrillation patients in general practice. Journal of Thrombosis and Haemostasis 2011; 9(1):39-48.

White HD, Gruber M, Feyzi J, *et al.* Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. *Archives of Internal Medicine 2*007;167(3):239-45.

Wolf PA, Abbott RD, Kannel WB. Atrial fi brillation as an independent risk factor for stroke: the Framingham study.*Stroke* 1991; 22: 983–88.