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Effectiveness of systematic screening for the detection of atrial fibrillation.

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Effectiveness of systematic screening for the detection of atrial fibrillation (Review)

Moran PS, Flattery MJ, Teljeur C, Ryan M, Smith SM

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[Intervention Review]

Effectiveness of systematic screening for the detection of atrial fibrillation

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ABSTRACT

Background

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is a leading cause of morbidity and mortality. Screening for AF in asymptomatic patients has been proposed as a way of reducing the burden of the disease by detecting people who would benefit from prophylactic anticoagulation therapy prior to the onset of symptoms. However, for screening to be an effective intervention it must improve the detection of AF and provide benefit for those who are detected earlier as a result of screening.

Objectives

The primary objective of this review was to examine whether screening programmes increase the detection of new cases of AF compared to routine practice. The secondary objectives were to identify which combination of screening strategy and patient population is most effective, as well as assessing any safety issues associated with screening, its acceptability within the target population and the costs involved.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library*, MEDLINE (Ovid) and EMBASE (Ovid) up to March 2012. Other relevant research databases, trials registries and websites were searched up to June 2012. Reference lists of identified studies were also searched for potentially relevant studies and we contacted corresponding authors for information about additional published or unpublished studies that may be relevant. No language restrictions were applied.

Selection criteria

Randomised controlled trials, controlled before and after studies and interrupted time series studies comparing screening for AF with routine practice in people aged 40 years and over were eligible. Two authors (PM, CT or MF) independently selected the trials for inclusion.

Data collection and analysis

Assessment of risk of bias and data extraction were performed independently by two authors (PM, CT). Odds ratios (OR) and 95% confidence intervals (CI) were used to present the results for the primary outcome, which is a dichotomous variable. Since only one included study was identified, no meta-analysis was performed.

Main results

One cluster randomised controlled trial met the inclusion criteria for this review. This study compared systematic screening (by invitation to have an electrocardiogram (ECG)) and opportunistic screening (pulse palpation during a general practitioner (GP) consultation for any reason followed by an ECG if pulse was irregular) to routine practice (normal case finding on the basis of clinical presentation) in people aged 65 years or older. The risk of bias in the included study was judged to be low.

Both systematic and opportunistic screening of people over the age of 65 years are more effective than routine practice (OR 1.57, 95% CI 1.08 to 2.26 and OR 1.58, 95% CI 1.10 to 2.29, respectively). The number needed to screen in order to detect one additional case compared to routine practice was 172 (95% CI 94 to 927) for systematic screening and 167 (95% CI 92 to 806) for opportunistic screening. Both systematic and opportunistic screening were more effective in men (OR 2.68, 95% CI 1.51 to 4.76 and OR 2.33, 95% CI 1.29 to 4.19, respectively) than in women (OR 0.98, 95% CI 0.59 to 1.62 and OR 1.2, 95% CI 0.74 to 1.93, respectively). No data on the effectiveness of screening in different ethnic or socioeconomic groups were available. There were insufficient data to compare the effectiveness of screening programmes in different healthcare settings.

Systematic screening was associated with a better overall uptake rate than opportunistic screening (53% versus 46%) except in the $\geq$ 75 years age group where uptake rates were similar (43% versus 42%). In both screening programmes men were more likely to participate than women (57% versus 50% in systematic screening, 49% versus 41% in opportunistic screening) and younger people (65 to 74 years) were more likely to participate than people aged 75 years and over (61% versus 43% systematic, 49% versus 42% opportunistic). No adverse events associated with screening were reported.

The incremental cost per additional case detected by opportunistic screening was GBP 337, compared to GBP 1514 for systematic screening. All cost estimates were based on data from the single included trial, which was conducted in the UK between 2001 and 2003.

Authors' conclusions

Systematic and opportunistic screening for AF increase the rate of detection of new cases compared with routine practice. While both approaches have a comparable effect on the overall AF diagnosis rate, the cost of systematic screening is significantly more than that of opportunistic screening from the perspective of the health service provider. The lack of studies investigating the effect of screening in other health systems and younger age groups means that caution needs to be exercised in relation to the transferability of these results beyond the setting and population in which the included study was conducted.

Additional research is needed to examine the effectiveness of alternative screening strategies and to investigate the effect of the intervention on the risk of stroke for screened versus non-screened populations.

PLAIN LANGUAGE SUMMARY

Screening people aged over 65 years for atrial fibrillation increases the rate of detection

Atrial fibrillation is a common cardiac arrhythmia that makes the heart beat rapidly and irregularly. This can occur for brief episodes or may be continuous. Symptoms of the disease include heart palpitations, chest pain, shortness of breath, light-headedness and fatigue. The condition is rare in those under 40 years but gets more common as people age. Not everyone with atrial fibrillation experiences symptoms so some people are unaware that they have it, while others may experience mild symptoms that they do not attribute to the disease. Atrial fibrillation hinders the efficient flow of blood through the heart, resulting in an increased risk of clot formation. If these clots leave the heart they can block the vessels supplying blood to the brain, causing a stroke. Treatment with anticoagulant medication is designed to prevent the formation of blood clots and can reduce the risk of stroke by over 60%.

For a screening programme for atrial fibrillation to be worthwhile it needs to increase the rate of detection as well as benefitting those who are detected with the problem through screening. The aim of this review was to examine the first part of this question, to find out if screening increases the number of new diagnoses of atrial fibrillation compared with normal practice where people are diagnosed when they consult a health professional with symptoms or risk factors that would lead to them being tested. It also examined the safety and rate of uptake of screening, as well as the costs involved.

The review identified one study that met the inclusion criteria. This examined systematic screening, where everyone over 65 years was offered an electrocardiogram (ECG) test, and opportunistic screening, where those over 65 years had their pulse taken when they visited their general practitioner (GP) for any reason and were offered an ECG if an irregular pulse was found. Both these screening

programmes increased the rate of detection of new cases of atrial fibrillation compared to normal practice. Screening appeared to be more effective in men than women but no information was available about its effectiveness in different ethnic or socioeconomic groups. Since only one study was found, it was not possible to compare the effectiveness of screening in different settings. Uptake of screening was higher for systematic screening than for opportunistic screening, and within both interventions the uptake was higher for men and the 65 to 74 age group compared to people over 75 years. No safety issues or complications were reported. From the point of view of the health service provider, systematic screening was more costly than opportunistic screening. However, because all of the results are based on a single study, one needs to be cautious about applying them outside of the setting (UK primary care) and patient population (aged over 65 years) in which the study was carried out.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Screening versus routine practice for the detection of atrial fibrillation

Patient or population: patients with the detection of atrial fibrillation
Settings:
Intervention: screening
Comparison: routine practice

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Routine practice	Screening				
Systematic Screening versus Routine Practice Number of new diagnoses Follow up: 12 months	**Study population**		**OR 1.56** (1.08 to 2.24)	9075 (1 study)	⊕⊕⊕◯ **moderate**[1]	
	10 per 1000	**16 per 1000** (11 to 23)				
	Moderate					
	10 per 1000	**16 per 1000** (11 to 22)				
Opportunistic Screening versus Routine Practice Number of new diagnoses Follow up: 12 months	**Study population**		**OR 1.57** (1.1 to 2.26)	9088 (1 study)	⊕⊕⊕◯ **moderate**[1]	
	10 per 1000	**16 per 1000** (11 to 23)				
	Moderate					
	10 per 1000	**16 per 1000** (11 to 22)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Given the nature of the intervention it was not possible to blind the participants in this study. No deliberate attempt to conceal allocation was made but failure to do this is not judged to introduce a risk of selective enrolment.

BACKGROUND

Screening for atrial fibrillation (AF) in asymptomatic patients has been proposed as a way of reducing the burden of stroke by detecting people who would benefit from prophylactic anticoagulation prior to the onset of symptoms of the arrhythmia (Harris 2012). The idea of screening for this condition is not new (for example Baxter 1998; Sudlow 1998; Wheeldon 1998), however there is renewed interest in the topic given the continued high incidence of stroke in many countries along with data showing that significant room for improvement remains in the identification and management of AF (Lip 2012). The overall evaluation of the benefits of a systematic screening programme for atrial fibrillation requires consideration of the probability of adverse health outcomes in the absence of screening, the degree to which screening identifies all people who would suffer these adverse health outcomes and the magnitude of incremental health benefits of earlier versus later treatment resulting from screening (Harris 2011). This review is related to the second of these three considerations; does systematic screening for AF in adults identify people with previously undiagnosed AF more effectively than routine practice?

Description of the condition

AF is the most common arrhythmia in clinical practice and is a leading cause of morbidity and mortality (Fuster 2006). The condition is characterised by predominantly uncoordinated atrial activation with consequent deterioration of atrial mechanical function. Some cases can be asymptomatic, while other people with AF may experience palpitations, chest pain, dizziness or, in severe cases, loss of consciousness (NCCCC 2006). The '3 P' system classifies AF according to the frequency of the attacks and whether they are self terminating or require pharmacological or medical cardioversion (Levy 2003). Using this classification system, AF in people who experience two or more episodes that terminate within seven days is classified as paroxysmal AF. If a person has more than one attack that lasts longer than seven days it is termed persistent AF. Finally, if the AF episode lasts for more than a year or cannot be terminated by cardioversion it is classified as permanent AF. The frequency of reoccurrence in paroxysmal AF can increase over time or may degenerate into persistent or eventually permanent AF (NCCCC 2006). Persistent AF as a result of an underlying heart condition can often be returned to normal sinus rhythm by treating the underlying cause. In addition to classifying AF in terms of the frequency of symptoms, different types of AF may be distinguished by the presence or absence of other underlying heart problems. Lone AF generally applies to individuals under 60 years of age without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension. Valvular and non-valvular AF describe whether associated disorders of the heart valves, including rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair, are present or absent (Fuster 2006).

In studies that included epidemiological data from the United Stated (US) and Australia, the prevalence of AF in the general population was estimated to be between 0.4% and 1% (Feinberg 1995; Go 2001). The prevalence of AF increases with age (Fuster 2006), rising from 2.3% in those over 40 years of age to around 8% in those over 80 years (Wolf 1991; Furberg 1994; Feinberg 1995). Prevalence estimates vary however, especially in the older age group, with some European epidemiological studies reporting a prevalence of approximately 17% in those aged $\geq$ 85 years (Heeringa 2006; Bilato 2009). The median age of AF patients is 75 years and 70% are between 65 and 85 years old (Feinberg 1995). Using data from the US and Canada, the corresponding incidence of AF for those under 40 years is less than 0.1% per year, rising to 1.5% in women and 2% in men older than 80 years (Wolf 1987; Krahn 1995; Psaty 1997).

Of particular importance in terms of systematic screening is the prevalence and risk profile of people with AF who have not been diagnosed, either because they are asymptomatic ('silent AF') or their symptoms remain unrecognised. It is estimated that one third of people with AF have no obvious symptoms (Furberg 1994; Savelieva 2000). However, assessing the prevalence of this type of AF is challenging since episodes of the arrhythmia may be brief, completely asymptomatic and difficult to detect (Savelieva 2000), and people experiencing mild symptoms may attribute them to other causes. In the absence of systematic screening, asymptomatic AF is diagnosed incidentally through routine physical examinations, pre-operative assessments or after complications such as stroke or heart failure have occurred. The Framingham Study found that among patients who had a stroke due to AF, the arrhythmia was first diagnosed in 24% of cases (Wolf 1983). A later report by the same group showed that 18% of participants who experienced stroke related to AF were newly diagnosed following admission, and another 4.4% were diagnosed with paroxysmal AF within 14 days (Lin 1995). It has been suggested that silent AF may also be associated with silent cerebral infarcts; in one study (Cullinane 1998) silent embolic signals were detected by transcranial Doppler in 13% of patients with symptomatic AF and 16% of those with asymptomatic AF. The relationship between asymptomatic AF or AF with few symptoms and the development of cardiomyopathy was investigated by Grogan et al (Grogan 1992), who found a significant improvement in left ventricular function after restoration of sinus rhythm or adequate ventricular rate response during AF. In this study of people who had little or no awareness of their arrhythmia and only sought medical attention when symptoms of heart failure developed, it was concluded that asymptomatic and undiagnosed AF may cause, rather than result from, severe left ventricular dysfunction. The idea that the risk profile and subsequent clinical management of symptomatic AF may also extend to asymptomatic AF is consistent with the findings of other studies which have shown that the type of AF (sustained versus paroxysmal) does not impact on risk of stroke or non-central nervous system (non-CNS) embolism (Hohnloser 2007)

and that continuous anticoagulation is warranted in all patients with atrial fibrillation and risk factors for stroke even when sinus rhythm appears to be restored and maintained (Wyse 2002).

AF is associated with an increased risk of stroke, congestive heart failure, cognitive dysfunction, reduced quality of life and all cause mortality (Ott 1997; Benjamin 1998; Stewart 2002). The mortality rate among people with AF is about double that among those with normal sinus rhythm and is linked to the severity of the underlying heart disease (Kannel 1983; Flegel 1987; Krahn 1995). AF contributes to an increased risk of stroke due to haemodynamic instability caused by irregular fast heartbeat and thromboembolic complications. For non-valvular AF populations the two-year age-adjusted incidence of stroke and thromboembolism is increased five-fold (Wolf 1991). This risk increases with age; the Framingham Study estimated that the annual risk of stroke attributable to AF in people aged 50 to 59 years was 1.5%, which rose to 23.5% in people aged 80 to 89 years (Wolf 1991). In addition, stroke due to AF is almost twice as likely to be fatal compared to stroke in the absence of AF and results in greater functional impairment for those who survive (Lin 1996). CHADS2, and more recently CHA2DS2-VASC, are clinical prediction rules that have been used to estimate the risk of stroke in AF and to recommend anticoagulation therapy based on risk factors such as age, sex and clinical history. A CHADS score of ≥ 1, corresponding to an annual risk of stroke of 2.8%, indicates that anticoagulation therapy should be considered (ESC 2010).

The last 20 years have seen a 66% increase in hospitalisations due to AF, and AF currently accounts for one third of all hospitalisations for cardiac rhythm disturbances (Freiberg 1997; Stewart 2001; Wattigney 2003; Fuster 2006). This is due to population ageing, the rising prevalence of chronic heart disease and advances in diagnosis. The condition is also associated with high economic costs to the individual and society. It is estimated that the annual cost per patient is approximately EUR 3000, while the total societal cost in the EU is about EUR 13.5 billion (Fuster 2006).

Description of the intervention

Systematic screening programmes for AF differ from routine practice by offering tests for AF to a wider range of people then those who present in routine consultations with symptoms, risk factors or other indications for AF testing. A systematic approach would define which test to use in conjunction with which screening strategy in order to increase the diagnosis of AF in the community, including patients with asymptomatic AF or those who are symptomatic but remain undiagnosed. A screening strategy of opportunistic pulse taking or ECG recording during a routine consultation is treated as a type of systematic screening strategy if all patients who are offered the test are identified a priori and the intervention is offered regardless of the reason for the consultation. The current gold standard test to detect AF is a 12-lead ECG interpreted by a cardiologist (Hobbs 2005). Other tests that can be used may involve alternative types of ECG (limb lead, three-lead, five-lead) read by a general practitioner (GP) in combination with preliminary pulse palpation carried out by a physician or nurse. Pulse palpation, however, is not conclusive on its own (Cooke 2006). Due to the intermittent nature of paroxysmal AF, either frequent repeated electrocardiograms (where the arrhythmia is present at the time of the test) or continuous ambulatory ECG monitoring tests are sometimes required (Go 2001). These diagnostic tests can be employed using a range of screening strategies, including opportunistic, targeted and population based screening. Opportunistic screening usually involves pulse palpation during the course of a routine medical consultation, with recourse to ECG if an irregular pulse is detected. Targeted or structured screening involves the identification of certain groups considered to be at higher risk of having AF or groups that can otherwise be singled out for screening. Finally, there is the option of conducting population based screening programmes where screening is offered to everyone in a particular population who has not previously been diagnosed with AF.

Screening programmes can differ in the population screened, the testing regime used and the health professionals carrying out the tests and interpreting the results. Some interventions described previously have involved either one or two step processes, depending on whether ECG was used on its own or in conjunction with pulse palpation, with the population tending to be those over 65 years of age. Nurse led pulse palpation, ECG recording by physicians or ECG technicians and interpreted by physicians and cardiologists have been reported. For example, Wheeldon et al (Wheeldon 1998) used a one step strategy, inviting all people aged over 65 years within a primary care practice for a single 12-lead ECG performed by an ECG technician and interpreted by a hospital cardiologist. In another study, Morgan and Mant (Morgan 2002) randomised patients over 65 years to either nurse led pulse palpation or opportunistic pulse palpation prompted by a reminder flag on their medical records, with irregular pulse findings in both arms being confirmed using a lead II rhythm strip interpreted by a general physician.

The costs associated with systematic screening have been examined in a number of published studies and are dependent on the screening strategy used and the health system within which they are implemented. Hobbs et al (Hobbs 2005) calculated UK costs for opportunistic screening, systematic screening in high risk populations and population based systematic screening (all in those over 65 years) and found that the incremental cost per additional case detected compared to no screening was lowest for opportunistic screening (GBP 337, GBP 3520 and GBP 1514, respectively). Maeda et al (Maeda 2004) calculated the incremental cost of annual ECG screening for patients between 65 and 85 years of age compared to no screening in Japan to be approximately USD 125 for men and USD 150 for women.

How the intervention might work

Systematic screening for AF in general adult populations could potentially increase diagnosis rates by identifying people with asymptomatic AF as well as those who are symptomatic but remain undiagnosed because of failure to attribute symptoms to the arrhythmia and to seek medical attention. A systematic screening programme creates a broader window for diagnosis compared to routine practice since it tests people prior to the occurrence of symptoms or complications. Therefore, such an intervention may result in greater numbers of people being diagnosed, or receiving an earlier diagnosis compared with routine practice, as the time period within which AF is occurring is likely to be correlated with diagnosis, and AF can begin prior to the advent of symptoms or complications, or both (Wolf 1983; Cullinane 1998; Savelieva 2000). The effectiveness of the intervention depends on a number of factors, including the prevalence of undiagnosed AF, choice of screening strategy and its acceptability to the patient population, as well as the costs associated with the intervention.

Given the relatively high prevalence of AF in older populations, and the increased morbidity and mortality associated with it, a screening programme that increased the rate of detection of AF has the potential to reduce the incidence of adverse cardiovascular events in this high risk population. Earlier diagnosis of AF will help identify those who would benefit from oral antiplatelet or anticoagulant prophylaxis, calculated to reduce the relative risk of stroke in patients with AF by approximately 20% and 60%, respectively (Hart 2007; ESC 2010). However, even if systematic screening is shown to increase the rate of detection of AF, it will still be necessary to evaluate the magnitude of the overall clinical benefits and harms in order to avoid bias associated with screening (for example over-diagnosis, length-time bias) and to prevent inaccurate conclusions being drawn about the effectiveness of treatment in patients who are identified through systematic screening programmes. Also, since the cardiovascular risk profile of screen detected people may be lower than that of those who present with symptoms and co-morbidities caused by AF, the balance of risk (adverse event) and benefit (stroke avoided) associated with prophylactic treatment would likely be altered.

It has also been pointed out previously (Hobbs 2005) that screening for AF meets many of the Wilson-Jungner (Wilson Jungner 1968) criteria for screening for disease. The condition is an important health problem and there is an accepted treatment for people following diagnosis and a suitable test or examination exists. One of the secondary aims of this review is to examine the evidence for some of the other screening criteria, such as the acceptability of the test to the population and the cost of case-finding, which should be economically balanced in relation to possible expenditure on medical care as a whole.

Why it is important to do this review

AF is under-diagnosed and under-treated, especially in the elderly (Hobbs 2005; ESC 2010; Ogilvie 2010). The condition lends itself to screening since testing is considered to be relatively inexpensive and efficient in terms of the follow up required. The primary objective of systematic screening is to reduce the risk of disease within a population through early detection, so that patients can receive treatment to improve their clinical outcomes. This review addresses the first part of that objective, namely the extent to which screening can be reasonably assumed to increase detection. Given the existing evidence in relation to the clinical benefit to be gained from treatment of AF, including asymptomatic AF, a systematic screening programme would seem to be an attractive option if it could be shown to increase the rate of detection compared to routine practice. The size of this benefit is unclear since data specifically relating to screen detected patients are unavailable, however randomised controlled trial (RCT) data on the primary prevention of ischaemic stroke in AF patients using a vitamin K antagonist compared to controls indicates a relative risk reduction of 67% (ESC 2010).

This review does not examine the evidence in regard to the degree of benefit, in terms of cardiovascular events avoided or increased quality of life, that can result from earlier diagnosis. Nor does it specifically seek to find out if those identified through systematic screening programmes are more or less likely to eventually suffer the adverse consequences associated with the arrhythmia than those diagnosed through routine practice. While these issues may be examined in further research, it is important to know first of all whether or not the use of systematic screening succeeds in its primary objective of increasing the detection rate of AF in the general population. If the introduction of systematic screening programmes fail to increase the detection rate for AF, there can be no subsequent change in health benefits and the other criteria need not be examined. On the other hand, if there is an increase in the rate of detection then subsequent treatment of these patients may reduce their individual risk of experiencing adverse cardiovascular events and reduce the overall burden of the disease within the health systems that introduce such a programme.

OBJECTIVES

This review aims to answer the following questions.

1. Does systematic screening increase the detection of AF compared to routine practice?

The primary objective of the review was to investigate whether there is evidence of a difference in the detection of new cases of AF between systematic screening and routine practice. Clinical outcomes associated with having received an earlier diagnosis and

subsequent treatment are not within the scope of this review. Earlier detection is assumed to result in improved outcomes within the screened population, as it is generally accepted that effective treatments exist to manage symptoms and reduce the risk of stroke for those with a diagnosis of AF.

2. Which combination of screening population, strategy and test is the most effective at detecting AF compared to routine practice?

Evidence for the effectiveness of different types of screening programmes was compared to find out which method detects AF more effectively. For screening programmes that were shown to be more effective than routine practice, the magnitude of the benefit in terms of overall numbers of new AF cases detected and the number needed to screen in order to detect one additional case compared to routine practice were calculated.

3. What are the potential safety issues and adverse events associated with individual screening programmes?

In any systematic screening programme for AF, a large number of people will be tested in order to identify a small number who have the arrhythmia. Therefore, any harms associated with screening will affect a much larger proportion of the screened population than the proportion who will experience the benefits associated with being diagnosed. This review assesses the safety and adverse events associated with individual screening programmes. The potential harms depend on the type of screening involved but can include complications associated with testing, anxiety generated by the screening process, as well as inconvenience associated with investigation and follow up. Potential harms occurring after diagnosis are not assessed in this review; these may include adverse events related to treatment, such as haemorrhagic stroke, unnecessary treatments as a result of over-diagnosis, or adverse effects of labelling or early diagnosis.

4. How acceptable is the intervention to the target population?

One of the most important factors affecting the effectiveness of a screening programme is the participation of the target group. If a screening programme is unacceptable to the target population, uptake is likely to be low (Jepson 2000). Evidence in regard to the acceptability of individual screening programmes to both the healthcare professionals and the screening population involved was evaluated. Factors that may affect acceptability include anticipated or actual pain, discomfort or embarrassment, or if a positive diagnosis is followed up by an intervention or treatment that is considered to be unacceptable (Jepson 2000). Costs incurred by the patient over the course of the screening process are included in the acceptability analysis on the basis that higher costs deter patients from participating in screening programmes (Frazier 1990).

5. What are the costs associated with systematic screening for AF?

Direct costs from the perspective of the healthcare provider were assessed in order to provide data on the practicalities of implementing individual programmes, in terms of likely resource allocation, compared to routine practice. Since an overall analysis of the magnitude of the health benefits and harms will not be carried out, the cost data reported were limited to the incremental costs of screening compared no screening and the costs per additional case identified, where such information was available.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCT) and cluster randomised controlled trials (cluster-RCT) comparing systematic screening to routine practice were eligible for inclusion, irrespective of language or publication status.

Quasi-experimental study designs (controlled before and after (CBA) studies and interrupted time series (ITS) studies) comparing systematic screening to routine practice were eligible for inclusion, subject to the criteria stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Box 6.3.a) (Higgins 2011) and criteria developed by the Cochrane Effective Practice and Organisation of Care (EPOC) Group (EPOC 2011). ITS studies were only to be included if the numbers of people in the pre and post-intervention populations were reported. Due to the nature of the intervention, it was considered appropriate to include non-randomised study designs and analyse these separately. Large scale population based screening programmes could potentially be evaluated in well designed CBA and ITS studies with a high degree of external validity in circumstances where randomisation is not feasible.

Case series, cohort studies, studies that use historical controls or cross-sectional studies were excluded.

Results from randomised studies were reported separately to results from quasi-experimental studies, where applicable.

Studies comparing more than one systematic screening programme were eligible for inclusion as long as there was a control arm of routine care included in the study.

Types of participants

Men and women over the age of 40 years. Epidemiological data indicate that AF is extremely uncommon prior to age 40 years, with the two-year AF incidence in the absence of rheumatic heart disease estimated at 0.04% for men and 0% for women aged 30 to 39 years (Wolf 1987). Therefore, younger participants were excluded due to the extremely low incidence of AF in this population, which would render systematic screening unfeasible, and to avoid inclusion of studies involving specific patient groups (for example paediatric or elite athletes) where the aetiology, diagnosis and subsequent clinical management of AF may differ from age-related onset of AF. Studies that included patients with implantable pacemakers or defibrillators or a previous diagnosis of AF in the control and intervention group were eligible for inclusion as long as these patients were excluded from the final number of newly diagnosed cases of AF reported.

Types of interventions

Studies eligible for inclusion compared population based, targeted or opportunistic screening programmes to no screening, where the control or pre-intervention (for ITS studies) group relied on routine practice for the diagnosis of AF over the relevant time period. The method of detecting AF in the intervention group could consist of single or multi-step processes but the diagnosis needed to be ultimately confirmed using 12-lead or continuous ambulatory ECG interpreted by a GP, specialist or suitably trained ECG technician or nurse in both the intervention and control (or pre-intervention) groups. Interventions that used pulse palpation alone or other types of ECG reading to confirm a diagnosis of AF were excluded.

Routine practice (control group) was defined as diagnoses made during routine care, either incidentally or following presentation with indications for AF testing, that were subsequently confirmed using 12-lead or continuous ambulatory ECG interpreted by a GP, specialist or suitably trained ECG technician or nurse. In addition, there had to be a clear mechanism for recording the number of new diagnoses of AF made over the relevant study period in this group. Opportunistic screening, where all members of the intervention group had their pulse recorded during the course of a routine consultation for any reason, was differentiated from routine practice where AF diagnoses were made following presentation with symptoms of an arrhythmia, or incidentally through other examinations, but where specific AF testing for all patients was not mandated. Studies that only used an alternative systematic screening strategy, instead of routine practice, as the control were not eligible for inclusion.

Types of outcome measures

Primary outcomes

The primary outcome being investigated was the difference in the detection of new cases of AF associated with systematic screening compared to routine practice, for individual screening programmes identified as being eligible for inclusion in the review and where a diagnosis of AF was defined as a positive reading using a 12-lead or continuous ambulatory ECG interpreted by a specialist, physician or suitably trained ECG technician or nurse. This information was used to calculate the overall difference in the numbers of AF cases detected compared to routine practice, as well as the number needed to screen (NNS) in order to detect one additional case of AF within the population. If studies describing multiple different systematic screening programmes had been identified, then AF detection rates for each were to be ranked according to their effectiveness when compared to routine practice. This was only to be calculated using data from studies that provided a clear denominator. In the case of RCT and CBA studies, this would be the numbers of people in the intervention or control groups, making sure that patients with a prior AF diagnosis were excluded. For ITS studies, data were only to be included if a clear denominator (number of patients in post-interrupt group) was reported.

Secondary outcomes

1. Acceptability of systematic screening programmes within the target population

Acceptability of screening was 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.

The level of uptake of a systematic screening programme was defined as the percentage of the screening population that participated in the full screening programme. For screening strategies that involve more than one stage (for example pulse palpation followed by ECG), uptake was defined as those who completed both stages. Data relating to the level of uptake among subgroups of the overall population were also reported for individual screening programmes.

Issues in regard to the acceptability of the intervention to the patient or health professional, or both, may depend on the type of screening programme involved. They were eligible for inclusion if based on primary data collected through the use of questionnaires, interviews or other means of eliciting the experience and opinions of the participants or health professionals involved. A narrative summary of the issues affecting the acceptability of different types of screening programmes was provided.

Costs incurred by the patient taking part in the screening programme were described as part of the analysis of the acceptability of the intervention to the patient, with higher costs being assumed to be less acceptable than lower or no costs.

2. Adverse events associated with systematic screening programmes

The rate and severity of complications or adverse events associated with ECG or other forms of AF testing were 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. Analysis of the costs associated with systematic screening programmes for AF

Only direct costs from the perspective of the healthcare provider were included in the analysis of this outcome. Where possible, a description of the operational and training costs associated with screening was provided along with the incremental cost of screening and cost per additional case detected compared with a policy of no screening.

4. Changes to the known prevalence of AF

Using data from patients included in cluster-RCTs and CBA studies, an estimate of the prevalence of AF within the screening population was calculated. Data from studies that do not provide a clear denominator, which may be the case with some ITS studies especially, were not included in the calculation of this outcome. Data from RCTs, CBA and ITS studies that did not report the numbers of patients who had a prior diagnosis of AF were not included in the calculation of this outcome.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 3 of 12) on *The Cochrane Library*, MEDLINE (Ovid) (1948 to February week 4 2012) and EMBASE and EMBASE Classic (Ovid) (1947 to Week 11 2012) for RCTs (Appendix 1), CBA and ITS studies (Appendix 2) on 22 March 2012.

The Cochrane RCT filter (sensitivity maximising) was applied to MEDLINE and terms used by The Cochrane Collaboration to limit a search to RCTs in EMBASE were applied to EMBASE (Lefebvre 2011). The EPOC methods filter was applied to MEDLINE and EMBASE to limit the searches for the other included study designs.

Searching other resources

The following databases, trials registries and websites were also searched for relevant studies up to 1st June 2012:

CINAHL (via EBSCO), 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 Center Freiburg, EU Clinical Trials Register, German Clinical Trials Register, Iranian Registry of Controlled Trials, Japanese NIPH Clinical Trials Registry, UMIN-CTR (Japan), Nederlands Trial Register, Pan African Clinical Trials Registry, Sri Lanka Clinical Trials Registry, Australia New Zealand Clinical Trials Registry, Brazilian Clinical Trials Registry, Chinese Clinical Trials Registry, Korean Clinical Research Information Service, Clinical Trials Registry India) and the websites of Eurostroke (European Stroke Conference), EHRA and ACC (see Appendix 3 for the search terms used in each of these resources).

Reference lists of all included papers were searched to identify potentially relevant articles. Where required, we contacted lead authors and investigators for information about additional published or unpublished studies that may be relevant.

No date or language restrictions were applied to any of the searches.

Data collection and analysis

Selection of studies

Preliminary screening of all returned results was carried out by a single author (PM) to eliminate studies which were clearly not relevant. Assessment of eligibility of studies and identification of multiple reports from single studies were carried out independently by two authors (PM and either CT or MF). Disagreements were resolved by discussion or, if necessary, by a third author (either CT or MF).

Data extraction and management

Data extraction was performed independently by two authors (PM and CT). Disagreements were resolved by discussion or, if necessary, by a third author (MF).

The following data were extracted from included studies.

1) All relevant data pertaining to the study characteristics and the primary and secondary outcomes of interest.

This included the study setting, number of centres, funding, patients characteristics, screening method and AF test used, number of patients in each arm, AF cases detected, patient uptake, factors affecting participation, quality of life data related to screening, other adverse events or complications, prevalence of AF in the study population, and cost data related to screening.

2) All data required in order to perform risk of bias assessment.

This included study design, allocation method, blinding procedures if any, patient withdrawals, reporting of all outcomes, and risk of contamination. Studies were examined for other potential

threats to the validity of their findings that were specific to the particular trial design and clinical setting.

Assessment of risk of bias in included studies

Two authors (PM and CT) independently assessed the risk of bias in included studies in accordance with the guidelines stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This was determined using the Collaboration's risk of bias tool included in section 8.5 of the handbook, which categorises studies as either high risk of bias, low risk of bias or unclear risk of bias.

Risk of bias in ITS and CBA studies was to be assessed using methods developed by the Cochrane Effective Practice and Organisation of Care (EPOC) Group (Suggested risk of bias criteria for EPOC reviews). CBA risk of bias criteria include analysis of the methods used for participant selection, study performance, AF detection and reporting of results. ITS risk of bias criteria include analysis of whether the intervention was independent of other changes, if the shape of the intervention effect was pre-specified and if the intervention was unlikely to affect data collection.

This review was not subject to some types of bias associated with screening (for example lead-time bias) since the primary outcome was a difference in the rate of detection as opposed to survival or time to event data. Biases associated with screening studies that could result in incorrect conclusions being drawn are length time and over-diagnosis bias. Length time is a form of selection bias where patients with slowly progressing AF are more likely to be identified by screening than people for whom the onset of symptoms and associated adverse cardiovascular events are more acute. This is because of the longer time period within which people are asymptomatic but would test positive for AF, making them more likely to be picked up by screening. Similar to lead-time bias, this can make it appear that cases discovered through screening fare better than those that present with symptoms, but in reality the difference is not due to screening but because screening disproportionately identifies slowly progressing AF. Despite the fact that no time-to-event data were included, there is a risk to this review from length-time bias arising from overestimation of the benefit of screening by assuming that all identified cases will derive the same benefit from anticoagulation prophylaxis to reduce the risk of stroke when in fact the patients who would benefit the most (that is those with more severe, rapidly progressing AF) are least likely to be identified through screening. This is also the case for paroxysmal AF, which is likely to be more difficult to detect through screening than is persistent or permanent AF. However, available evidence suggests that stroke risk in these two groups are similar (Friberg 2010). A similar situation exists with regard to over-diagnosis bias, where the implementation of a screening programme may result in asymptomatic AF patients being diagnosed and treated when in the absence of a screening programme they may never have become symptomatic or suffered a stroke as a result of the arrhythmia. However, these biases do not introduce systematic errors into the primary outcome of concern in this review (AF diagnosis rate), rather they may lead to over-interpretation of the clinical gains associated with increasing the detection of AF through systematic screening.

Studies were assessed for other sources of bias that may be relevant to specific methods used in the performance of the research. For instance some screening programmes involve a two step process to test for AF, with manual pulse palpation being performed initially followed by an ECG if an irregular pulse is found. Since the accuracy of pulse palpation is affected by the skill and experience of the medical practitioner (Hobbs 2005), there is the potential for an intervention bias related to variations in the proficiency of different health professionals performing the test, which would influence the results of the study. However as this is not a review of diagnostic test accuracy, as long as the intervention specifies the type of reader used it will be possible to avoid inappropriate comparisons across studies. Other types of bias that were to be considered, depending on the type of study involved, included compliance bias if the intervention or control group involved self initiated testing by the patient, which can lead to outcomes being driven by how compliant the participants are rather than the effectiveness of the screening intervention (Fletcher 2005). Studies were assessed on an individual basis for other potential sources of bias.

Measures of treatment effect

The effect of systematic screening was measured by the difference in the number of cases of AF detected between the control and intervention groups divided by the number of cases in each group. Differences were expressed as the overall magnitude of the difference in the AF detection rate between the intervention and control or pre-intervention groups as well as the number needed to screen (NNS) in order to detect one additional case of AF within the population.

Pooled analysis of treatment effect was to be carried out using standard meta-analytic techniques, provided enough study data were obtained and taking account of heterogeneity between studies. Fixed-effect model meta-analysis would be performed initially, with the option of using random-effects model meta-analysis if a moderate or high degree of heterogeneity was observed between studies. As a summary measure of effectiveness, odds ratios (OR) with 95% confidence intervals (CI) were calculated for dichotomous variables.

Results from studies describing different screening interventions were not pooled and the results from randomised and non-randomised studies were to be reported separately.

Unit of analysis issues

Cluster-randomised trials were assessed in order to ensure that appropriate analysis was carried out to address cluster effects and to avoid overestimating the significance of differences. In cluster-

randomised studies where the analysis was carried out as if the randomisation was performed on the individuals rather than the clusters, efforts were to be made to obtain the data needed to correct for this, as described in section 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For controlled trials that compared more than one screening method the meta-analysis of each method was to be performed separately to avoid counting the control group twice.

Dealing with missing data

Lead investigators or corresponding authors were contacted for any missing data or for additional clarification.

Assessment of heterogeneity

An assessment of the heterogeneity of included studies was to be performed if sufficient data were available to perform a meta-analysis. I^2 values above 75% are considered to have exceeded the level of heterogeneity appropriate for drawing meaningful conclusions from pooled data. Chi^2 tests for heterogeneity were also planned to be performed and data were to be considered heterogeneous if $P < 0.10$. Significant statistical heterogeneity was to be investigated, along with the clinical heterogeneity of the populations across included studies.

Assessment of reporting biases

Studies were assessed to check if all relevant outcomes in the study protocol were reported in the final results, per the risk of bias heading 'selective outcome reporting'. Any outcomes specified in the methods that were omitted from the results were taken as evidence that outcomes were selectively reported. In the event of evidence of selective reporting authors were to be contacted to enquire if the results were reported elsewhere (that is published in another paper or otherwise available). Asymmetry of the funnel plot based on the data for the primary outcome would be taken as an indication of publication bias.

Data synthesis

A narrative of the results of included studies is provided along with information on their risk of bias. A meta-analysis of similar studies to produce a combined estimate of the effect was planned if multiple studies were identified, subject to acceptable levels of statistical and clinical heterogeneity. Differences between the results of fixed-effect and random-effects model meta-analysis would require re-examination of the clinical and methodological diversity of the pooled studies before making a judgment on which would be the most appropriate statistical model to use. In the event that insufficient data were available to perform a meta-analysis, effect sizes and confidence intervals of each outcome from the included study were to be reported individually.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was to be performed on the following groups subject to the availability of sufficient data.

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.

Subgroups were identified a priori based on a plausible rationale supported, where possible, by published literature. The number of subgroups was kept to a minimum and priority was given to subgroups that are of specific interest to the potential implementation of a systematic screening programme.

The primary subgroup examined was the effectiveness of the intervention in the over 65 years age group. The comparator for this subgroup was people over 65 years for whom no screening programme was introduced. This group is of relevance for two reasons. Firstly, one of the features of an ideal screening programme in primary care is that there is a sufficiently high prevalence of the disease in the screened population to justify screening (Goroll 1995). The prevalence of AF increases substantially with age (Wolf 1991; Feinberg 1995; Go 2001). The median age of AF patients is 75 years and 70% are between 65 and 85 years old. Therefore a screening programme in this group is likely to be more effective given the higher baseline prevalence of the condition compared to the overall population included in the review. The second reason why the over 65 age group is important is because they are a recognised group within most public health systems, thus providing an opportunity to capitalise on existing structures to effectively target a public health initiative such as a screening programme.

Given the increasing prevalence of AF with age, it may be logical to assume that the older the age group targeted by the screening programme the more effective it will be. To investigate this issue, a separate subgroup analysis of people aged 65 to 75 years versus those > 75 years was conducted in order to compare the effectiveness of systematic screening in an older population within the group for which screening is most likely to be implemented in practice (that is all over 65 years).

The effectiveness of systematic screening in men versus women was also examined in the subgroup analysis since there are a number of reasons to presume that gender could influence the effectiveness of a screening programme for AF. Men are 1.5 times more likely than women to develop the disease (Benjamin 1994) and this may make screening in men more effective given the higher underlying prevalence. In addition to this, there are factors relating to the potential differences in the uptake of any screening programme in men and women that could impact on outcomes. The direction of this effect is uncertain, however. It has been reported that men are more reluctant than women to contact their GPs and other healthcare services (Peate 2004). In another study in the US (CDC 2001) it was found that despite excluding pregnancy-related visits,

women were 33% more likely than men to visit a doctor, although this difference decreased with age. However, others have reported (Wardle 2005; Friedemann-Sanchez 2007) that men are more likely to attend colorectal cancer screening than women. Since the rate of uptake of screening is such an important factor in determining the success of a screening programme (Barratt 2002; Parkin 2008) it is worthwhile to separately investigate the differences in reported outcomes for men and women.

Apart from gender, ethnicity and social deprivation are the two main factors found to influence population based cancer screening programmes in the UK (Weller 2009). This review had also planned to include subgroup analysis of the effectiveness of screening in different ethnic and socioeconomic groups, if these were reported, in order to provide useful data that could be relevant to readers of the review. There are risks involved since the practice of including data on outcomes only if they are reported can lead to the introduction of bias as significant results are more likely to get published than non-significant results. However it was anticipated that, due to the established importance of these factors, the reporting of data on ethnicity and socioeconomic status would more than likely be carried out for large population based screening programmes where it is appropriate and is unlikely to be reported in studies where the participant population or screening approach is incompatible with such an analysis. Despite this, it had been planned to clearly explain the limitations of any available data and the caveats associated with subgroup interpretation in the reporting of the review had it been possible to conduct this analysis.

The final subgroup that was to be examined relates to the setting within which the screening programme was conducted. It is possible that studies of screening strategies carried out within the community or in primary care could have been identified along with studies based in specialist settings like hospitals or other secondary care facilities. Given the importance of the setting to any consideration of how a major screening programme could be implemented within a health system, it was considered important to provide an analysis of any differences in the reported outcomes associated with the setting. The setting could affect how well a screening programme performs in a number of ways. The acceptability of the clinical settings where systematic screening takes place to the person to whom the test is offered can affect the rate of uptake and settings within the community, such as GP or public health nurse led programmes, may be more acceptable, and therefore more effective, for people who are used to receiving care in these settings. As with the ethnicity and socioeconomic subgroups, this subgroup analysis was only be performed if it was considered appropriate to do so after consideration of the studies included in the review.

Sensitivity analysis

Depending on the studies obtained from the systematic search, a sensitivity analysis was to be conducted to calculate the effect of risk of bias within studies on effect size by calculating the effect of excluding or including studies with a higher risk of bias.

RESULTS

Description of studies

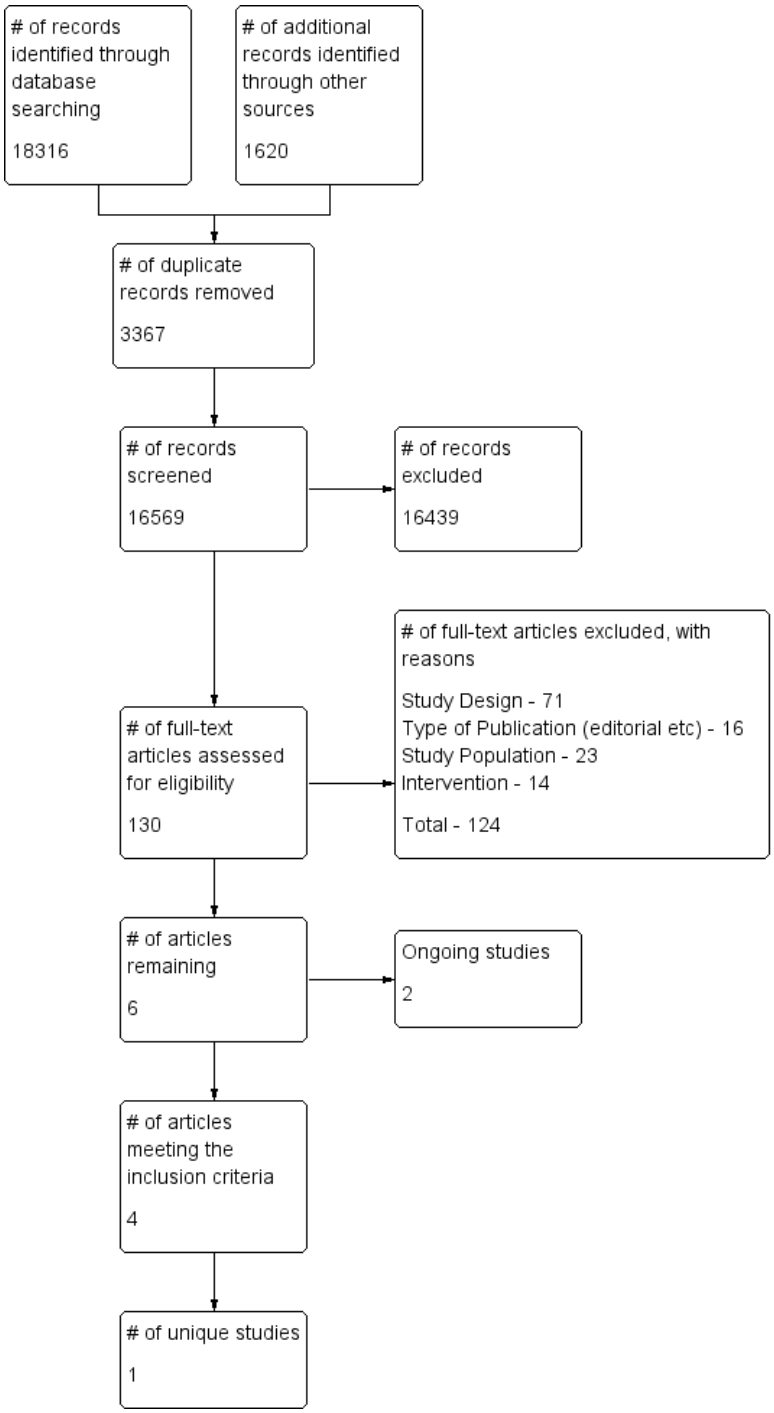
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

One (cluster) randomised controlled trial (cluster-RCT) met the inclusion criteria (Hobbs 2005). No eligible controlled before and after (CBA) studies or interrupted time series (ITS) studies were identified. Two potentially relevant studies that are currently ongoing were also identified (NCT01593553; NCT01291953).

Results of the search

We identified 19,936 citations during the search. After removal of duplicates and screening out irrelevant studies, 130 citations were reviewed independently by two authors (PM and CT or MF). This produced four citations that met the inclusion criteria (Swancutt 2004; Hobbs 2005; Fitzmaurice 2007; Mant 2007), all of which were based on the same study (Hobbs 2005). See Figure 1 for more details. Seven authors were contacted during the review process to enquire if they had conducted additional research in this area since the publication of their last article, or if they knew of other studies that may be eligible for inclusion. Despite a high rate of response (5/7) no further studies were identified that met the inclusion criteria.

Figure 1. Study flow diagram.



Included studies

The single study that met the inclusion criteria for this review was a cluster-randomised trial comparing screening of those aged 65 years or over to routine practice in the primary care setting in the UK (Hobbs 2005). A total of 25 general practices with computerised record keeping systems were randomised to either the control or intervention groups. Randomisation was stratified according to practice size and level of deprivation (Townsend score). All practices within the intervention group received educational materials highlighting the importance of AF detection and the range of treatment options available. Healthcare professionals within these practices were encouraged to consider opportunistic pulse taking during routine consultation. In total, 10,000 patients aged 65 years or older were randomly selected from the intervention practices and allocated equally between two different screening interventions embedded within the intervention arm. These were systematic screening, where patients were invited by letter to attend an ECG screening clinic, or opportunistic screening, where patients' GP records were flagged to prompt the GP to check the pulse whenever that patient next attended the practice for any reason. Health professionals in control practices received no training; 5000 patients aged 65 years or older were randomly selected from this group for follow up as a comparator group receiving routine care.

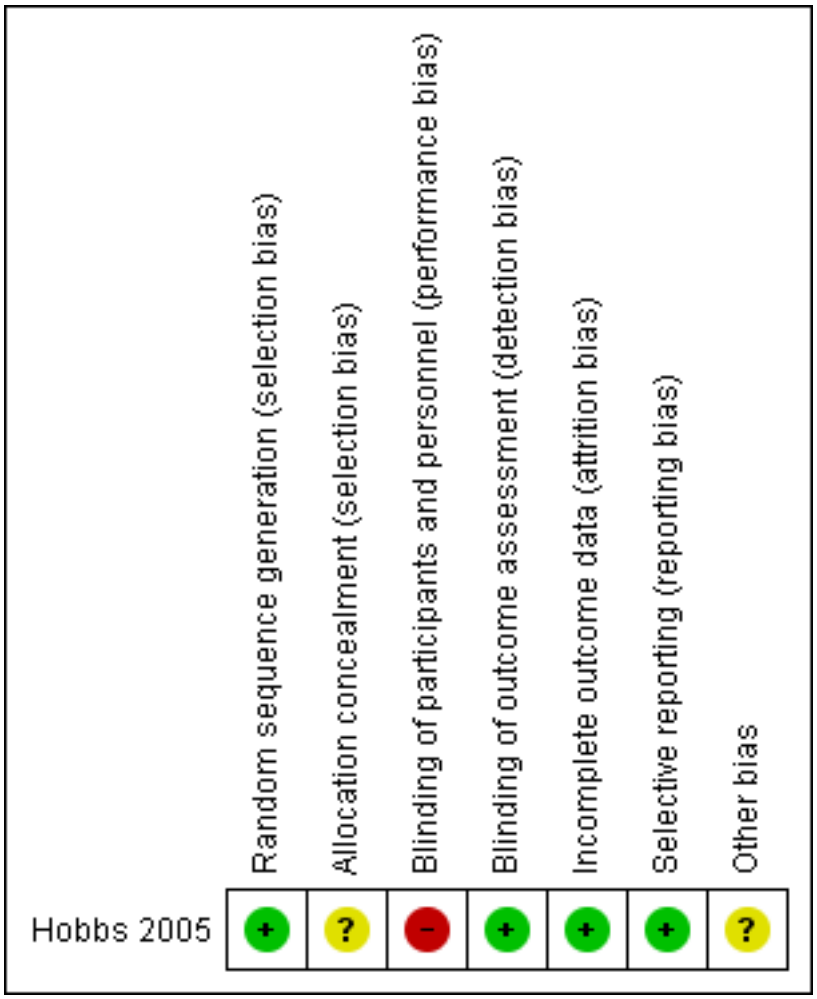
Excluded studies

Fifteen studies examining screening for AF did not meet the inclusion criteria for this review (Baxter 1998; Sudlow 1998; Wheeldon 1998; Munschauer 1999; Somerville 2000; Ho 2004; Morgan 2002; Maeda 2004; Hoefman 2005; Wright 2007; DeRuijter 2008; Johnson 2010; Marek 2011; Claes 2012; ACTRN12612000406808). The reasons for their exclusion are described in the Characteristics of excluded studies section.

Risk of bias in included studies

Since only one study met the inclusion criteria, this review is limited to summarising risk of bias for that study across outcomes, with particular reference to the primary outcome of differences in the rate of detection of AF. A summary of the risk of bias assessment is shown in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The randomisation methods used to allocate patients in the included study resulted in a low risk of bias since all centres were randomised at the same time, and the intervention and control groups were not known at the point of randomisation. Within the treatment group, patients were selected using computer generated random numbers and the lists were stratified on the basis of numbers of patients with an existing diagnosis of AF, which resulted in each arm having a comparable chance of detecting known, unknown or suspected AF. There was no deliberate concealment of allocation to the trial arms but the clusters (GP practices) were identified and recruited before randomisation was conducted, so allocation was concealed from the people providing permission for the cluster to be included in the trial. Similarly, patients in the intervention arm were identified and randomly allocated into two groups before it was known to anyone involved in the trial which group would be allocated to which treatment (opportunistic or systematic). However, since there was no deliberate attempt to conceal allocation it is unclear to what extent a risk of selection bias might have arisen from practices in the intervention arm knowing they were in the intervention arm and not the control arm prior to the recruitment of participants. See the Characteristics of included studies table for more information.

A separate issue is the potential for self selection bias inherent in screening studies in which patients decide whether or not to undergo testing. However, given the randomisation methods that were used and the intention-to-treat analysis performed the risk of bias associated with this is considered to be low.

Blinding

Given the nature of the intervention it was not possible to blind the participants in the included study. In the systematic screening arm patients were invited to attend an ECG clinic. One of the factors contributing to the outcome of the intervention was the rate of uptake of this invitation, which was a decision that had to be made by individual patients who were provided with adequate information to make an informed decision. In the opportunistic screening arm the records of patients were flagged to prompt clinicians to offer to palpate the pulse of patients who presented in the GP practice for any reason. In this arm, patients also needed to be informed about the intervention and to decide whether or not to participate. Therefore blinding of patients and GPs as a method of reducing the likelihood of performance bias was neither achievable or desirable given the intervention. See the Characteristics of included studies table for more information.

Detection bias was minimised by blinding the two consultant cardiologists who read the 12-lead ECG about whether the ECG was from patients who had received an invitation for screening (n = 2357) or were referred following the detection of an irregular pulse (n = 238). All ECG tracings were taken by practice nurses who were probably not blinded to which treatment arm individual patients were in.

Incomplete outcome data

There was a significant difference in the numbers of patients excluded by GPs from the systematic and opportunistic arms of the trial following randomisation. Five hundred patients (10.1%) in the systematic arm and 195 patients (4%) in the opportunistic arm had either died, moved away from the practice area, or were terminally ill or otherwise unsuitable for screening. The risk of bias associated with this was low, however, since the same criteria were used to exclude patients in both arms of the intervention and 98% of the withdrawals from the systematic group were due to patients having died (246 patients) or moved away (245 patients). An intention-to-treat analysis was used to calculate differences in the rate of detection of new cases of AF between the different arms, which used the number of patients in each arm prior to these withdrawals. Only patients with a pre-existing diagnosis of AF (7.2%) and patients whose notes were missing (0.6%) were excluded from the calculation. See the Characteristics of included studies table for more information.

The notes of all patients within each group were searched at the end of the study to identify all those who had been diagnosed with AF over the course of the trial, including those in the intervention groups that had been diagnosed outside of the screening programme. These diagnoses were included in the analysis of the primary outcome.

Selective reporting

There was no suggestion of selective reporting in the included study. All outcomes specified in the trial protocol (Swancutt 2004) were reported.

Other potential sources of bias

There was an unclear risk of recruitment bias emanating from the fact that after initial randomisation, lists of patients were given to GPs to exclude patients who were unsuitable for screening, and these patients were replaced from a back-up list that had been generated as part of the original randomisation process. No data were provided on the numbers from each group who were replaced at this stage. GPs were instructed to remove people who had died, moved away, or were terminally ill. Significant differences in the numbers excluded from each arm may have indicated differences in the way these criteria were applied by practice GPs across the two groups, potentially introducing bias. Data from the second round of exclusions, which was performed immediately prior to screening, resulted in the removal of 10% of people from the systematic arm compared to 4% from the opportunistic arm (see Incomplete outcome data (attrition bias) section above).

Effects of interventions

See: **Summary of findings for the main comparison** Screening versus routine practice for the detection of atrial fibrillation; **Summary of findings 2** Systematic screening compared to opportunistic screening for the detection of atrial fibrillation

For the primary outcome of detection of new cases of AF, results from the single included study showed that both systematic and opportunistic screening of people over the age of 65 years for AF in primary care was more effective than routine practice (OR 1.57, 95% CI 1.08 to 2.26; Analysis 1.1 and OR 1.58, 95% CI 1.10 to 2.29; Analysis 1.2, respectively). There was no significant difference between systematic and opportunistic screening in terms of the number of new cases detected (OR 0.99, 95% CI 0.72 to 1.37; Analysis 2.1). The number needed to screen in order to detect one additional case compared to routine practice was 172 (95% CI 94 to 927) for systematic screening and 167 (95% CI 92 to 806) for opportunistic screening. When gender subgroups were analysed the results indicated that both systematic and opportunistic screening were more effective in men (OR 2.68, 95% CI 1.51 to 4.76 and OR 2.33, 95% CI 1.29 to 4.19, respectively) than in women (OR 0.98, 95% CI 0.59 to 1.62 and OR 1.2, 95% CI 0.74 to 1.93, respectively), see Analysis 1.3 and Analysis 1.5. The difference between the gender subgroups was statistically significant for systematic screening (Chi^2 = 6.64, P = 0.01; I^2 = 84.9%) but not for opportunistic screening (Chi^2 = 2.95, P = 0.09; I^2 = 66.1%). Subgroup analysis by age (65 to 74 years, 75 +) failed to show significant differences in the detection of new cases of AF between participants in these two age ranges, see Analysis 1.4 and Analysis 1.6. See Table 1 for the numbers of new cases of AF diagnosed in each group and by gender and age group. No data

were reported on different ethnic groups. No association between socioeconomic status and the effectiveness of systematic or opportunistic screening was reported.

The acceptability of the screening intervention was measured by the rate of uptake of screening, feedback from participants and health professionals, as well as the cost associated with screening from the point of view of the patient. For systematic screening an invitation was considered accepted if the patient attended an ECG screening clinic following the receipt of the letter. For opportunistic screening a patient was considered to have participated in the programme if they agreed to have their pulse taken opportunistically during a routine consultation and subsequently accepted an offer of an ECG if an irregular pulse was found. This differed from the analysis carried out within the included study, which considered uptake on the basis of those who agreed to have their pulse taken, even if they declined to have an ECG if an irregular pulse was found. The rationale for taking a different approach in this review was that since ECG confirmation was required to make a diagnosis, patients for whom this was indicated who did not proceed to have an ECG could not be said to have taken up the offer of screening since they had not completed the full two stage process. Uptake results are shown in Table 2. Systematic screening was associated with a greater overall rate of uptake than opportunistic screening, with a higher rate of uptake of systematic screening being seen in both men and women. This trend was also observed in the 65 to 74 years age group, but for those aged over 75 years the uptake rates for both interventions were similar. Overall men were more likely to participate in screening than women, and people from the younger age group (65 to 74 years) were more likely to participate than those aged 75 years and over. A questionnaire concerning the acceptability of screening was administered to all patients undergoing an ECG within the intervention arm: 95% of those who completed this felt that screening was important (1810/1897); 17% (324/1897) felt that they didn't know what was involved; and 4% (70/1897) felt it wasn't convenient. Mean costs incurred by patients undergoing ECG were GBP 3.13 (95% CI 2.97 to 3.29, range GBP 0.65 to 14.53).

No specific adverse events associated with screening were reported. Anxiety levels and quality of life were measured at baseline and at the end of the study using the six-item Spielberger state anxiety inventory and the five-item EQ-5D. A total of 750 questionnaires were distributed to patients in the intervention arm prior to screening. Six hundred and twenty were returned: 311 from opportunistic patients (55 not completed) and 309 from systematic patients (72 not completed). No significant difference was found between the two intervention arms at baseline for anxiety ($z = -0.392$, $P = 0.695$) or quality of life ($z = -0.334$, $P = 0.739$). A total of 777 post-screening questionnaires were distributed and 630 were returned, 535 of which were completed: 479 of these completed the six-item Spielberger state anxiety questions, and 520 competed the five-item EQ-5D questions. No significant difference was found between the two intervention arms at the end of the study for anxiety ($z = -1.699$, $P = 0.089$) or quality of life ($z = -1.166$, $P = 0.244$). End of study anxiety scores for screen-positive and screen-negative patients were significantly different ($F(1268) = 4.883$, $P = 0.028$). Patients diagnosed with AF had a higher anxiety score (38.12, 95% CI 35.89 to 40.35 versus 34.61, 95% CI 32.41 to 36.81) and a lower quality of life score (0.66, 95% CI 0.59 to 0.70 versus 0.73, 95% CI 0.68 to 0.77).

An economic analysis carried out as part of the single included study found that when costs were examined from the perspective of a national health service provider (National Health Service (NHS) in this case) the incremental cost of the estimated 28 additional cases detected using opportunistic screening compared to no screening was GBP 9429 (95% CI 8938 to 9920), giving an incremental cost per additional case detected of GBP 337. The incremental cost of the estimated 27 additional cases detected using systematic screening compared to no screening was GBP 40,882 (95% CI 39,790 to 41,974), giving an incremental cost per additional case detected of GBP 1514. All cost estimates were based on the trial data, and the trial was conducted in the UK between 2001 and 2003.

AF prevalence results from the included study are presented in Table 3. This table shows the baseline and 12-month prevalence of AF within the study population in the control and intervention arms, with a breakdown of prevalence by gender and age group (65 to 74, 75 to 84, $\geq$ 85 years).

There was insufficient data to compare the effectiveness of screening programmes in different healthcare settings

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Systematic screening compared to opportunistic screening for the detection of atrial fibrillation

Patient or population: patients with the detection of atrial fibrillation
Settings:
Intervention: systematic screening
Comparison: opportunistic screening

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Opportunistic screening	Systematic screening				
Systematic versus Opportunistic Screening Number of new diagnoses Follow up: 12 months	**Study population**		**OR 0.99** (0.72 to 1.36)	9137 (1 study)	⊕⊕⊕◯ **moderate**[1]	
	16 per 1000	**16 per 1000** (12 to 22)				
	Moderate					
	16 per 1000	**16 per 1000** (12 to 22)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Given the nature of the intervention it was not possible to blind the participants in this study. No deliberate attempt to conceal allocation was made but failure to do this is not judged to introduce a risk of selective enrolment.

DISCUSSION

Summary of main results

Only one study met the eligibility criteria for this review (Hobbs 2005). No studies examining screening in populations under 65 years were identified. Two ongoing studies were identified that are likely to be of relevance to this review in the future (NCT01593553; NCT01291953). Based on the results of one included study, this review found that both systematic and opportunistic screening increase the rate of detection of AF in those people aged 65 years and over compared with routine practice. There was no significant difference in the relative effectiveness of the two interventions, with approximately 170 patients needing to be screened in both groups in order to detect one additional case. Uptake rates were higher for systematic screening than for opportunistic screening. Given the additional resources needed to support population based systematic screening, the overall cost of this intervention is considerably more than that of opportunistic screening.

Overall completeness and applicability of evidence

The single identified study provides evidence on the effectiveness of screening for AF in people aged over 65 years, the acceptability of this intervention in the target population, and the costs associated with the intervention within a publicly funded primary care setting. However there is a lack of studies examining other potential screening strategies, younger populations and different healthcare settings.

Since the acceptability of the intervention is a key factor in its effectiveness, differences in regard to participation rates, a patient's perception of screening, and direct costs to the patient in different settings means that caution needs to be exercised in relation to the transferability of the results. The uptake rate in the overall study population for opportunistic screening was calculated based on the numbers of patients who agreed to have their pulse taken and to have an ECG if an irregular pulse was found; 34% of those that were found to have an irregular pulse declined an ECG and were therefore not considered to have been opportunistically screened since they did not complete the intervention. In the group who did not consent to an ECG, 46% (56/122) already had a diagnosis of AF. When only those without a baseline diagnosis of AF are used to calculate uptake the percentage of patients who are discovered to have an irregular pulse but decline an ECG is 27%. The reasons for such a high dropout rate between irregular pulse finding and ECG are unknown. If the uptake rate is calculated solely on the basis of a patient consenting to having their pulse taken opportunistically during a routine consultation, then the uptake rate increases to 69%. While low levels of uptake and completion of screening are a cause for concern, the uptake rate of the included study is high when compared with an earlier study within the same health system comparing systematic screening (via invitation to attend nurse led pulse palpation) to opportunistic screening (Morgan 2002) that recorded an uptake rate of 29% in the opportunistic arm based on those who presented for any reason and consented to have their pulse taken regardless of whether or not an ECG was subsequently used to confirm the diagnosis. Hobbs 2005 concluded that these differences in uptake were due to improved coverage attained over the 12 months period of the Hobbs 2005 study, compared to the Morgan 2002 study which ran over six months. An excluded study (Wheeldon 1998), which was also conducted in the primary care setting in England, invited all patients aged 65 years and over for a 12-lead ECG to screen for AF and reported an uptake rate of 85%. The uptake rate of ECG screening reported in this study, which was excluded due to the absence of a comparison group receiving routine care, differs considerably from that of the systematic screening arm in Hobbs 2005, which achieved an uptake rate of 53%. These differences provide an indication of the variability that can exist within and between different screening strategies.

Another factor requiring consideration is the percentage of diagnoses made outside of the actual screening programmes within the intervention arm in Hobbs 2005. Of the 74 new cases of AF identified in the systematic group, 22 (30%) were diagnosed outside of the screening programme over the 12 months of the study. For opportunistic screening, a greater proportion of the 75 newly identified cases were diagnosed outside of the screening programme (44/75, 59%) than within it (31/75, 41%). When calculations are based only on patients who received the screening intervention, systematic screening has a detection rate of 2.2% compared with 0.9% for opportunistic screening. This implies a detection rate for those who did not participate in screening of 1% and 3% for the systematic and opportunistic groups, respectively. The detection rate in non-participants in the systematic arm is similar to that observed in the control arm (both approximately 1%), a figure which contrasts with the significantly higher detection rate seen in non-participants in the opportunistic arm (approximately 3%). The reasons for these differences are unclear, but they do have potential implications for service providers considering the introduction of AF screening and for how such services should be evaluated following their introduction.

Subgroup analysis of data from the single included study indicate that the effectiveness of both screening interventions is different in men and women. When male and female subgroups are analysed separately, both systematic and opportunistic screening continue to show a significant effect on new case detection compared with routine practice in men. No difference between either systematic or opportunistic screening and routine practice is seen in the subgroup of women. Possible reasons for this include differences in the prevalence of AF in men and women, differences

in the rate of uptake, or differences in the overall numbers in each group, which would result in subgroups being underpowered to detect significant effects. However this study included more women than men in both intervention groups (1958 men compared with 2604 women in systematic group; 1941 men compared with 2634 women in opportunistic group; 1880 men compared with 2633 women in control group) so the female subgroup was better powered to detect differences. However, though the study included more women it was still underpowered to detect effect sizes of the magnitude seen in the overall study within the subgroup of women. The rate of uptake of screening was higher among men than women (57% versus 50% for systematic; 49% versus 41% for opportunistic), though more women agreed to have their pulses taken in the opportunistic arm (71% versus 67%). It has consistently been shown that there is a higher prevalence of AF in men than in women (Gowd 2012) and this is borne out in the baseline prevalences reported in this study (7.8% in males, 6.8% in females). Therefore the differences in effect observed between the subgroups of men and women could be due to a combination of higher prevalence and greater rates of participation among men. This finding may also have implications for the provision of AF screening programmes.

Other factors that may affect the transferability of these results are the direct patient costs associated with screening (which can affect uptake) and the prevalence of undiagnosed AF. While the direct costs to patients are low in a publicly funded screening programme, the coverage achievable with opportunistic screening where GP care is not provided free at the point of use may be lower than that reported in the included study, and funding models that subsidise GP care for a proportion of the population may also affect who benefits from screening (McGregor 2006). Within the NHS, financial incentives introduced since the completion of this study through the Quality and Outcomes Framework (QoF), which encourage GPs to diagnose AF, may limit the effectiveness of screening compared to no screening since the prevalence of undiagnosed AF may be lower now than in 2003, when this research was carried out. In addition, this type of incentive may prove more effective in terms of identifying cases of AF than a screening programme, or may alter the delivery and uptake of screening programmes. These issues need to be taken into account when considering the applicability of these results in a given healthcare setting.

The study that met the inclusion criteria for this review compared systematic screening via an invitation to attend an ECG clinic and opportunistic screening via pulse palpation during routine consultations. However, there are a range of other strategies that could be used to screen for the arrhythmia in a variety of settings. As no studies comparing these to routine practice were identified, this review is limited in terms of the screening interventions that could be compared. Alternative screening strategies that have been described in studies that were excluded include the use of self screening methods (Baxter 1998, Munschauer 1999), population based screening programme using a national media campaign to invite participants (Claes 2012), systematic screening where patients are invited for pulse palpation rather than an ECG (Morgan 2002), and opportunistic ECG recording (Caldwell 2012).

Quality of the evidence

There is a lack of studies comparing screening for AF to routine practice. Only one eligible study was identified (Hobbs 2005), which was judged to be of moderate quality.

Potential biases in the review process

A comprehensive search was carried out to identify RCTs, CBA and ITS studies that compared screening for AF to routine practice in a general population of people aged over 40 years. Authors of relevant published or ongoing studies were contacted to enquire about other studies in this area. Overall this search returned 19,936 citations which were inspected to identify relevant studies. Only one cluster-RCT met the inclusion criteria, and the population included in this study was aged 65 years and over. Given the meticulous search that was conducted, the potential for publication bias is considered low. The input of a third author to settle disagreements concerning inclusion of individual studies was not required and data from the included study were cross-checked by two authors (PM, CT).

Agreements and disagreements with other studies or reviews

A recent review of strategies for the detection of AF (Harris 2012) identified two studies (Morgan 2002; Hobbs 2005) examining the effectiveness of screening. The conclusions are in line with those of Hobbs 2005, recommending opportunistic screening in the general population and highlighting that while a 12-lead ECG remains the standard investigation, the cost-effectiveness of newer technologies requires further research.

The overall rate of detection of new cases of AF in both intervention groups and the control group in the Hobbs 2005 study was approximately 1.6% and 1% respectively. Two studies that were excluded due to the absence of a control arm in the study design also reported the rate of detection of new cases of AF over the course of the study. Morgan 2002 reported a new case detection rate of 0.8% for systematic screening via an invitation to attend nurse led pulse palpation and 0.4% for opportunistic pulse palpation; whereas Wheeldon 1998 reported a detection rate of 0.8% for systematic screening via an invitation to undergo a 12-lead ECG. Though these studies could not be included in this review, they provide some context in relation to the level of variability that exists between studies in this area.

AUTHORS' CONCLUSIONS

Implications for practice

Both systematic and opportunistic screening increase the rate of detection of new AF cases compared with routine practice in people over the age of 65 years in a primary care setting. In the absence of additional data, caution needs to be exercised in drawing conclusions about the relative effectiveness of systematic and opportunistic screening. Based on the included study, both approaches have a comparable effect on the overall AF diagnosis rate, with the cost of systematic screening being significantly more than that of opportunistic screening from the perspective of the health service provider. The potential contribution of the educational element of the intervention that occurred in both the systematic and opportunistic arms prior to screening should not be overlooked. This may have influenced the number of new cases detected outside of the screening programmes in both arms, something that was particularly important in the opportunistic screening group where 59% of new diagnoses were made outside of the screening programme itself. Systematic screening achieves a higher uptake rate than that of opportunistic screening since about a third of people who are found to have an irregular pulse when opportunistically screened decline a confirmatory ECG test. This may pose ethical issues with regard to treatment of patient for whom an irregular pulse is recorded but ECG confirmation is absent. Based on the available evidence, screening offered to males is more effective than screening among females compared with routine practice. The lack of studies investigating the effect of screening in other health systems and younger age groups means that caution needs to be exercised in relation to the transferability of these results beyond the setting and population in which the study was conducted.

Implications for research

Two trials are ongoing that may provide additional data relevant to this review question (NCT01291953; NCT01593553). Future studies should examine the effect of using different types of ECG technology and different readers, which may have important implications for both the clinical and cost effectiveness of systematic and opportunistic screening. In addition, high quality studies examining the effectiveness of alternative screening strategies (for example opportunistic ECG, self screening, etc) would help expand the evidence base in this area. Further research is also needed to investigate the effect of screening on clinical outcomes such as stroke, and in particular the effectiveness of anticoagulation in screen detected versus non-screen detected patients.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hobbs 2005

Methods	Multi-centre cluster-randomised controlled trial involving 50 (computerised) primary care centres across the West Midlands, UK, over a 12 month period. Randomisation was stratified by levels of deprivation (Townsend quartiles) and practice size. A subsidiary trial was embedded in the intervention arm, comparing two different screening strategies. Overall time period was from October 2001 to February 2003
Participants	Male and female patients over 65 years of age attending general practices in the UK. Age range was 65 - 98 years, average age of 73.5 years. A random sample of 10,000 patients from the intervention group were allocated randomly to either systematic or opportunistic screening. Randomisation was stratified according to whether or not AF had been previously diagnosed in order to have an equal prevalence of known AF on both arms. A random sample of 5000 was selected from the control population. After sampling, lists were returned to practices to remove those who had died, moved or were terminally ill. These were replaced from a back-up list which had been randomised at the same time as the initial list Final number of participants in control arm = 4963 from 25 general practices Final number of participants in intervention arms = 4933 for opportunistic screening and 4933 for systematic screening from 25 general practices Baseline AF prevalence in the control population higher than in the intervention populations (7.9% versus 6.9%)
Interventions	Training: Staff at primary care centres in the intervention arms were given training on the importance of AF detection, available treatment options, and were encouraged to consider opportunistic screening of patients. Staff at control centres were given no training. Practice nurses received ECG training prior to starting ECG clinics Systematic screening: All patients in the systematic screening arm were sent an invitation to attend a screening clinic along with an information sheet. Non-responders were sent a reminder Opportunistic screening: Patients in the opportunistic screening arm had their records flagged to encourage staff to undertake pulse recordings during routine consultation. Patients who had an irregular pulse were given an information sheet and invited to attend a screening clinic Screening clinics: Screening clinics were run by practice nurses, who took patient histories, checked radial pulse rate and whether it was regular or irregular, and recorded a 12-lead ECG. The patient was then asked to complete a questionnaire on the acceptability of the intervention. All 12-lead ECGs were sent to two cardiologists for reporting. If there was disagreement over the diagnosis a third cardiologist decided. Patients were informed of the results within two weeks
Outcomes	Primary outcomes: New cases of atrial fibrillation detected within the 12 month study period

Hobbs 2005 (*Continued*)

	Incremental cost per case detected Secondary outcomes: Cost-effectiveness of screening in the UK Community prevalence and incidence of AF Acceptability of AF screening and patient uptake
Funding	This research was funded by the NHS research and development health technology assessment programme (No 96/22/11)
Notes	Intention-to-treat analysis was performed, patients who already had a diagnosis of AF excluded from the calculation of newly detected cases

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Probably done for control and intervention groups "After stratification for practice size and deprivation (based on Townsend score) , we used MINITAB to select randomly two equal size groups from those practices within a particular stratum. We used a simulated value from a Bernoulli distribution, comprising two values equally likely to occur, to determine which group became the intervention arm (the other being the control arm)" Also probably done for embedded trial within the intervention arm: "We used SPSS to allocate patients randomly from this list to either systematic or opportunistic screening to create two equal size groups of patients within each stratum so that each strategy (systematic or opportunistic screening) had an equal chance of detecting known, unknown, and suspected atrial fibrillation (n=4933). Which group then became the systematic arm (the other being opportunistic) was again decided by using a simulated value from a Bernoulli distribution, comprising two values equally likely to occur."
Allocation concealment (selection bias)	Unclear risk	The authors state that "there was no deliberate concealment of allocation to the trial arms...the trial statistician determined allocation, which was implemented by the trial coordinator". However the clusters (GP practices) were identified and recruited be-

		fore randomisation was conducted, so allocation was concealed from the people providing permission for the cluster to be included in the trial. Similarly, patients in the intervention arm were identified and randomly allocated into two groups before it was known to anyone involved in the trial which group would be allocated to which treatment (opportunistic or systematic), since this was decided at the end of the randomisation process using a simulated value from a Bernoulli distribution, comprising two values equally likely to occur. However since there was no deliberate attempt to conceal allocation it is unclear to what extent a risk of selection bias might have arisen from practices in the intervention arm knowing they were in the intervention arm and not the control arm prior to the recruitment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind patients, who were notified by letter that they were being offered the opportunity to participate in an AF screening clinic or were encouraged to have their pulse recorded during routine consultation. Neither were primary care physicians and healthcare staff blinded, since the intervention arm received training where they were informed of the importance of detecting AF and its treatment. Practice nurses at screening clinics who took the patients' medical history, pulse and ECG were probably not blinded to whether the patient came from the systematic or opportunistic arm. Blinding is not feasible in a situation where well informed patients who need to decide whether of not they want to avail of screening are a key component of the systematic screening intervention. However since inability to blind a study is not equal to a blinded study, it is classified as high risk. Screening clinics were used to test patients from each group according to the same protocol and with the aid of a 12-lead ECG machine (Biolog)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding was performed where possible; cardiologists who interpreted the 12-lead ECG reading in order to make a diagnosis of AF were blinded as to the allocation of the patient from whom the ECG was taken
Incomplete outcome data (attrition bias) All outcomes	Low risk	After random sampling to identify participants from the cluster-randomised primary care centres, general practices were contacted to exclude people who had died, moved away or were terminally ill. These exclusions were randomly filled from a reserve list of 10% of the practice patients which was randomised at the same time as the original list. Immediately prior to sending screening invitations or flagging notes, the general practices were again contacted to exclude people who had since died, moved or were terminally ill and these exclusions were not replaced, with the numbers in each arm reported. The primary outcome was calculated taking the original figure using an ITT approach. Patients within each group who already had a diagnosis of AF were excluded from the calculation of the primary outcome (new cases detected). This necessitated a review of patient record to identify those with a pre-existing diagnosis. Records for some people in each of the groups were missing and are reported for each group individually. Both patients with AF and those with missing notes were excluded from the calculation of the rate of new cases detected
Selective reporting (reporting bias)	Low risk	All outcomes specified in the trial protocol were reported
Other bias	Unclear risk	There is the potential for recruitment bias and contamination in the study. Recruitment bias could have been introduced at the stage where general practitioners were asked to exclude unsuitable patients from the opportunistic and systematic screening arms within the intervention group. Advice was given to exclude those who had died, moved away or were terminally ill from both groups. People who were excluded at this stage were replaced from a back-up

		list of patients that had been randomised at the same time as the groups. No data are provided about how many from each group were replaced at this stage, nor is the breakdown of the reasons for their exclusion given. Immediately prior to the intervention GPs were again asked to exclude any patients who had died, moved away or were terminally ill from both groups. Data concerning exclusions at this stage are reported and there was a considerable difference in the numbers excluded between the two arms; 500 were excluded from the systematic screening arm (10% of the total) and 195 (4% of the total). However the individual reasons for exclusion from the systematic screening arm are also reported and only a small minority of these (9 people, 0.2% of total) were deemed unsuitable, as opposed to having died or moved away (491people, 9.9% of total). An ITT analysis was performed that included patients that were removed from the intervention group at this stage in the calculation of the primary outcome

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12612000406808	Ineligible study design - no control group. This is an ongoing non-randomised registered trial where community pharmacists will screen members of the general public for atrial fibrillation using a combination of a manual pulse check and a handheld single-lead ECG (using the AliveCor Heart Monitor for iPhone). This will be a once off screening of approximately 5-10 minutes duration. Following screening, the pharmacist will contact the participant's GP via letter, stating the provisional diagnosis. A cardiologist will review all of the single-lead ECG recordings to ensure the pharmacists interpretation is correct. The GP will be further contacted by the research team if the diagnosis is other than reported by the pharmacist. The screening trial will be conducted over a 6-month period
Baxter 1998	Ineligible study design - this was a pilot study of self screening for AF in an older population (age range 55-75 years). No controls were used and irregular pulse readings were not confirmed using ECG. Communication with corresponding author indicated that the study had not been continued further following this publication

(*Continued*)

Claes 2012	Ineligible study design - no control group. This report describes a study where "patients over 40 years were invited through different channels (TV, radio, journals, web site, posters, leaflets) for a free screening in 69 hospitals allocated over Belgium during one week. After filling in a question on their personal history of AF, they had to fill in a questionnaire about their CHAD2-score. Afterwards a one channel ECG was taken using a versatile Heart Scan Device (Omron HCG-801-E©) by a trained nurse or a physician. If the ECG was positive for AF the patient was referred to their physician for follow-up. " No control group receiving routine care was included or no time series data were recorded to examine the effect of the intervention compared with no screening. 10,758 people over 40 years participated, resulting in 167 new diagnoses of AF. When calculated on the basis of those who responded to the media campaign the detection rate for new cases of AF is approximately 1.56%. It is not possible to calculate the rate of detection based on the total number of people who received an invitation
DeRuijter 2008	Ineligible study design - this was a prospective cohort study to evaluate whether routinely performed ECGs in older people from the general population have added value for cardiovascular risk management beyond the information that is already available from their medical records
Ho 2004	Ineligible study design - no controls. In this study "500 subjects were drawn by two-stage random sampling from 5,002 subjects aged 70 years and over living at home. Subjects were screened for atrial fibrillation and left ventricular systolic dysfunction using electrocardiography and echocardiography." This was a prevalence study with no data on the effect of screening compared with routine care
Hoefman 2005	Ineligible population - participants in this study were consecutive patients presenting with unexplained symptoms suggestive of arrhythmia
Johnson 2010	Ineligible study design - no controls. This conference abstract describes a study that employed a strategy of random screening in a public venue (an inner city public market) to determine stroke risk. However no controls were used and results were not compared to multiple time points pre and post-intervention. No diagnoses of AF were made
Maeda 2004	Ineligible study design - this was an economic evaluation which modelled the clinical outcomes and costs associated with a screening programme in Japan
Marek 2011	Ineligible study design - this a retrospective cohort study of large-scale electrocardiographic screening of young adults
Morgan 2002	Ineligible study design - no controls. This was a randomised trial comparing two different screening strategies. Patients were randomised either to nurse led screening or to prompted opportunistic case finding. Irregular pulses found during opportunistic screening did not need to be confirmed by ECG. The study was carried out over a 6-month period. Uptake in the systematic screening arm was 73%, compared to 29% (for pulse palpation alone) in the opportunistic arm. The detection rate of new cases of AF in the systematic arm was 0.8%, compared with 0.4% in the opportunistic arm
Munschauer 1999	Ineligible study design - this study was designed to determine whether individuals taken from the general community could be taught to find and classify the pulse of another as very irregular, implying AF, or regular, implying normal sinus rhythm (NSR). No data on the effectiveness of a screening programme compared to routine practice were reported

(*Continued*)

Somerville 2000	Ineligible study design - this study compared different methods of identifying cases in general practice using patients over 65 recruited from a general practice. 56% of invitees accepted an invitation for testing (86/154) but no data were reported on the rate of detection of new cases. The study was not designed to investigate the effect of screening compared with routine practice
Sudlow 1998	Ineligible study design - no controls. This study compares three methods of diagnosing AF in a sample of 1235 over 65's invited from 9 general practices in the UK. The three methods of screening used were 1) checking for a digoxin prescription 2) pulse palpation and 3) limb lead ECG. Response rate was 74% (916/1235). No data on rate of new diagnoses were reported
Wheeldon 1998	Ineligible study design - all patients over 65 years of age from a single primary care practice with 4 GPs were invited to attend for a 12-lead ECG to detect AF. An uptake rate of 85% was achieved (1207/1422). The overall detection rate of new cases of AF was approximately 0.4%
Wright 2007	Ineligible study design - no controls. This study randomised primary care centres to either implementing AF or TIA guidelines. The type of AF testing that was associated with the AF guidelines was unclear but effects on the rate of diagnosis of new cases of AF was reported. However there was no control arm receiving routine care

Characteristics of ongoing studies *[ordered by study ID]*

NCT01291953

Trial name or title	Effectiveness of Early Detection of Atrial Fibrillation (FAMDAP)
Methods	Multi-centre cluster-randomised controlled trial. Primary care centre professionals will be randomised to either the intervention group or a control group involving routine practice
Participants	Men and women over 65 years of age who are attending a primary care centre for any reason. Patients with a prior diagnosis of AF will be excluded. Anticipated enrolment of 12,870 participants
Interventions	Opportunistic screening of people aged 65 year or more presenting at primary care services. Opportunistic screening will involve pulse taking and requesting an ECG if an irregular pulse is found
Outcomes	Primary outcome is the numbers of new diagnoses of AF using opportunistic screening versus routine practice
Starting date	January 2011
Contact information	Principal Investigator: Luis Angel Pérula de Torres, Andalusian Health Service, langel.perula.sspa@juntadeandalucia.es
Notes	Trial ongoing, protocol due to be submitted for publication. Estimated completion in late 2012 ClinicalTrials.gov identifier: NCT01593553

NCT01593553

Trial name or title	Systematic ECG Screening for Atrial Fibrillation Among 75 Year Old Subjects in the Region of Stockholm and Halland, Sweden
Methods	Randomised controlled trial
Participants	Men and women 75-76 years of age living in the region of Stockholm or Halland. Anticipated enrolment of 6500 participants
Interventions	ECG screening for atrial fibrillation with intermittent ECG recording for 14 days. Introduction of anticoagulants in the case of atrial fibrillation
Outcomes	Reduced incidence of stroke among 75 year old subjects.
Starting date	March 2012
Contact information	Anna Hollander, RN LicMedSci +46-8-51778214 anna.hollander@karolinska.se
Notes	Trial ongoing, estimated completion March 2019 ClinicalTrials.gov identifier: NCT01291953

DATA AND ANALYSES

Comparison 1. Detection of new cases of atrial fibrillation versus routine practice

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systematic Screening versus Routine Practice	1	9075	Odds Ratio (M-H, Fixed, 95% CI)	1.57 [1.08, 2.26]
2 Opportunistic Screening versus Routine Practice	1	9088	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [1.10, 2.29]
3 Gender Subgroups (Systematic)	1	9075	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [1.08, 2.26]
3.1 Men	1	3838	Odds Ratio (M-H, Fixed, 95% CI)	2.68 [1.51, 4.76]
3.2 Women	1	5237	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.59, 1.62]
4 Age Subgroups (Systematic)	1	9075	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [1.09, 2.29]
4.1 Aged 65-74 years	1	5034	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [0.90, 2.91]
4.2 Aged >74 years	1	4041	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [0.97, 2.50]
5 Gender Subgroups (Opportunistic)	1	9088	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [1.10, 2.29]
5.1 Men	1	3821	Odds Ratio (M-H, Fixed, 95% CI)	2.33 [1.29, 4.19]
5.2 Women	1	5267	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.74, 1.93]
6 Age Subgroups (Opportunistic)	1	9088	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [1.12, 2.33]
6.1 Aged 65-74 years	1	5100	Odds Ratio (M-H, Fixed, 95% CI)	1.63 [0.91, 2.92]
6.2 Aged > 74 years	1	3988	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [1.00, 2.57]

Comparison 2. Detection of new cases of atrial fibrillation versus other screening

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systematic versus Opportunistic Screening	1	9137	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.72, 1.37]
2 Gender Subgroups	1	9137	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.71, 1.36]
2.1 Men	1	3899	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.74, 1.79]
2.2 Women	1	5238	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.50, 1.33]
3 Age Subgroups	1	9137	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.71, 1.36]
3.1 Aged 65-74 years	1	5190	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.60, 1.64]
3.2 Aged > 74 years	1	3947	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.64, 1.48]

Analysis 1.1. Comparison 1 Detection of new cases of atrial fibrillation versus routine practice, Outcome 1 Systematic Screening versus Routine Practice.

Review: Effectiveness of systematic screening for the detection of atrial fibrillation

Comparison: 1 Detection of new cases of atrial fibrillation versus routine practice

Outcome: 1 Systematic Screening versus Routine Practice

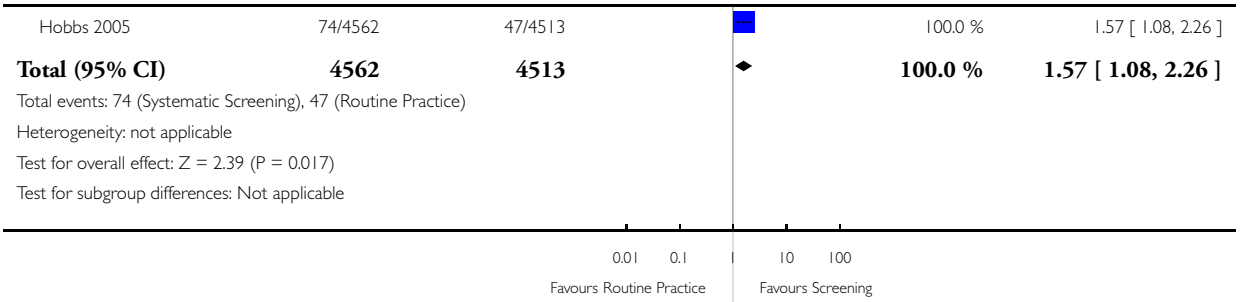
Study or subgroup	Systematic Screening n/N	Routine Practice n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Hobbs 2005	74/4562	47/4513		100.0 %	1.57 [1.08, 2.26]
Total (95% CI)	**4562**	**4513**		**100.0 %**	**1.57 [1.08, 2.26]**

Total events: 74 (Systematic Screening), 47 (Routine Practice)

Heterogeneity: not applicable

Test for overall effect: Z = 2.39 (P = 0.017)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Detection of new cases of atrial fibrillation versus routine practice, Outcome 2 Opportunistic Screening versus Routine Practice.

Review: Effectiveness of systematic screening for the detection of atrial fibrillation

Comparison: 1 Detection of new cases of atrial fibrillation versus routine practice

Outcome: 2 Opportunistic Screening versus Routine Practice

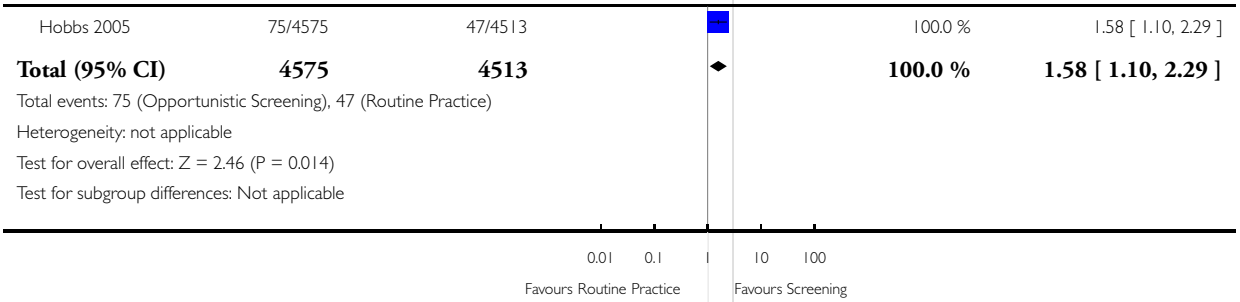
Study or subgroup	Opportunistic Screening n/N	Routine Practice n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Hobbs 2005	75/4575	47/4513		100.0 %	1.58 [1.10, 2.29]
Total (95% CI)	**4575**	**4513**		**100.0 %**	**1.58 [1.10, 2.29]**

Total events: 75 (Opportunistic Screening), 47 (Routine Practice)

Heterogeneity: not applicable

Test for overall effect: Z = 2.46 (P = 0.014)

Test for subgroup differences: Not applicable



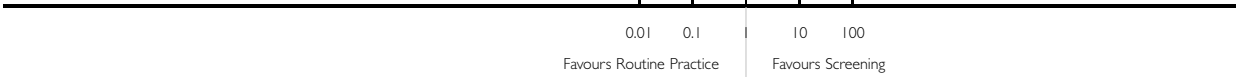
Analysis 1.3. Comparison 1 Detection of new cases of atrial fibrillation versus routine practice, Outcome 3 Gender Subgroups (Systematic).

Review: Effectiveness of systematic screening for the detection of atrial fibrillation

Comparison: 1 Detection of new cases of atrial fibrillation versus routine practice

Outcome: 3 Gender Subgroups (Systematic)

Study or subgroup	Systematic Screening n/N	Routine Practice n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Men					
Hobbs 2005	44/1958	16/1880		34.4 %	2.68 [1.51, 4.76]
Subtotal (95% CI)	**1958**	**1880**		**34.4 %**	**2.68 [1.51, 4.76]**
Total events: 44 (Systematic Screening), 16 (Routine Practice)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.35 (P = 0.00080)					
2 Women					
Hobbs 2005	30/2604	31/2633		65.6 %	0.98 [0.59, 1.62]
Subtotal (95% CI)	**2604**	**2633**		**65.6 %**	**0.98 [0.59, 1.62]**
Total events: 30 (Systematic Screening), 31 (Routine Practice)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
Total (95% CI)	**4562**	**4513**		**100.0 %**	**1.56 [1.08, 2.26]**
Total events: 74 (Systematic Screening), 47 (Routine Practice)					
Heterogeneity: Chi^2 = 6.67, df = 1 (P = 0.01); I^2 =85%					
Test for overall effect: Z = 2.37 (P = 0.018)					
Test for subgroup differences: Chi^2 = 6.64, df = 1 (P = 0.01), I^2 =85%					



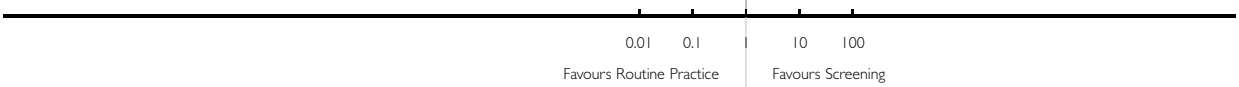
Analysis 1.4. Comparison 1 Detection of new cases of atrial fibrillation versus routine practice, Outcome 4 Age Subgroups (Systematic).

Review: Effectiveness of systematic screening for the detection of atrial fibrillation

Comparison: 1 Detection of new cases of atrial fibrillation versus routine practice

Outcome: 4 Age Subgroups (Systematic)

Study or subgroup	Systematic Screening n/N	Routine Practice n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Aged 65-74 years					
Hobbs 2005	30/2562	18/2472		39.2 %	1.62 [0.90, 2.91]
Subtotal (95% CI)	**2562**	**2472**		**39.2 %**	**1.62 [0.90, 2.91]**
Total events: 30 (Systematic Screening), 18 (Routine Practice)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.60 (P = 0.11)					
2 Aged >74 years					
Hobbs 2005	44/2000	29/2041		60.8 %	1.56 [0.97, 2.50]
Subtotal (95% CI)	**2000**	**2041**		**60.8 %**	**1.56 [0.97, 2.50]**
Total events: 44 (Systematic Screening), 29 (Routine Practice)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.84 (P = 0.065)					
Total (95% CI)	**4562**	**4513**		**100.0 %**	**1.58 [1.09, 2.29]**
Total events: 74 (Systematic Screening), 47 (Routine Practice)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 2.44 (P = 0.015)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.93), I^2 =0.0%					

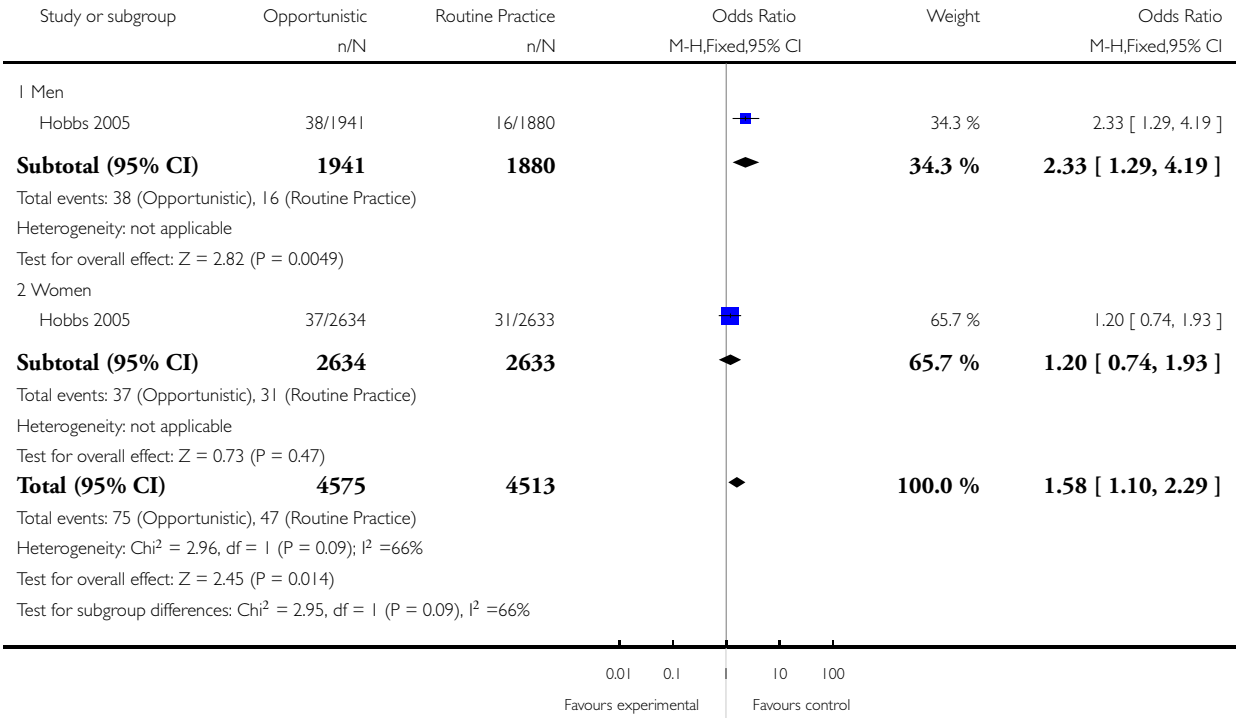


Analysis 1.5. Comparison 1 Detection of new cases of atrial fibrillation versus routine practice, Outcome 5 Gender Subgroups (Opportunistic).

Review: Effectiveness of systematic screening for the detection of atrial fibrillation

Comparison: 1 Detection of new cases of atrial fibrillation versus routine practice

Outcome: 5 Gender Subgroups (Opportunistic)



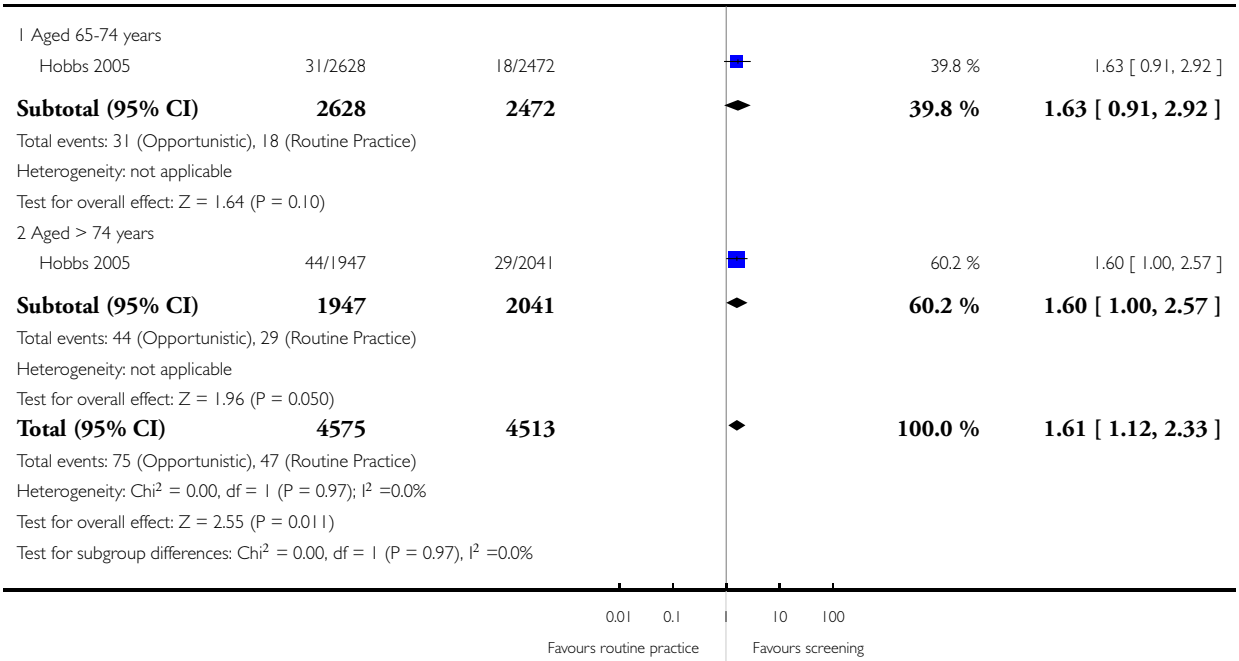
Analysis 1.6. Comparison 1 Detection of new cases of atrial fibrillation versus routine practice, Outcome 6 Age Subgroups (Opportunistic).

Review: Effectiveness of systematic screening for the detection of atrial fibrillation

Comparison: 1 Detection of new cases of atrial fibrillation versus routine practice

Outcome: 6 Age Subgroups (Opportunistic)

Study or subgroup	Opportunistic n/N	Routine Practice n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Aged 65-74 years					
Hobbs 2005	31/2628	18/2472		39.8 %	1.63 [0.91, 2.92]
Subtotal (95% CI)	**2628**	**2472**		**39.8 %**	**1.63 [0.91, 2.92]**
Total events: 31 (Opportunistic), 18 (Routine Practice)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.64 (P = 0.10)					
2 Aged > 74 years					
Hobbs 2005	44/1947	29/2041		60.2 %	1.60 [1.00, 2.57]
Subtotal (95% CI)	**1947**	**2041**		**60.2 %**	**1.60 [1.00, 2.57]**
Total events: 44 (Opportunistic), 29 (Routine Practice)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.96 (P = 0.050)					
Total (95% CI)	**4575**	**4513**		**100.0 %**	**1.61 [1.12, 2.33]**
Total events: 75 (Opportunistic), 47 (Routine Practice)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 2.55 (P = 0.011)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.97), I^2 =0.0%					



Analysis 2.1. Comparison 2 Detection of new cases of atrial fibrillation versus other screening, Outcome 1 Systematic versus Opportunistic Screening.

Review: Effectiveness of systematic screening for the detection of atrial fibrillation

Comparison: 2 Detection of new cases of atrial fibrillation versus other screening

Outcome: 1 Systematic versus Opportunistic Screening

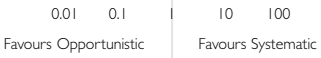
Study or subgroup	Systematic n/N	Opportunistic n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Hobbs 2005	74/4562	75/4575		100.0 %	0.99 [0.72, 1.37]
Total (95% CI)	**4562**	**4575**		**100.0 %**	**0.99 [0.72, 1.37]**

Total events: 74 (Systematic), 75 (Opportunistic)

Heterogeneity: not applicable

Test for overall effect: Z = 0.07 (P = 0.95)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Detection of new cases of atrial fibrillation versus other screening, Outcome 2 Gender Subgroups.

Review: Effectiveness of systematic screening for the detection of atrial fibrillation

Comparison: 2 Detection of new cases of atrial fibrillation versus other screening

Outcome: 2 Gender Subgroups

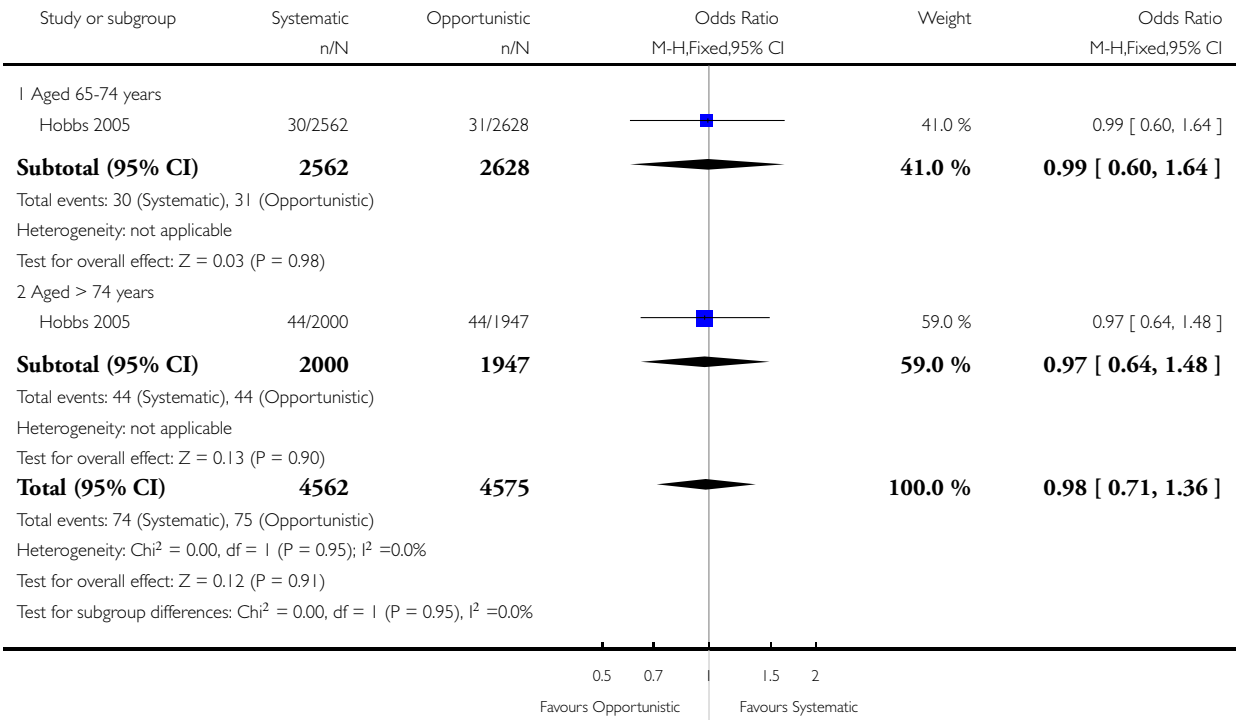
Study or subgroup	Systematic n/N	Opportunistic n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Men					
Hobbs 2005	44/1958	38/1941		50.6 %	1.15 [0.74, 1.79]
Subtotal (95% CI)	**1958**	**1941**		**50.6 %**	**1.15 [0.74, 1.79]**
Total events: 44 (Systematic), 38 (Opportunistic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
2 Women					
Hobbs 2005	30/2604	37/2634		49.4 %	0.82 [0.50, 1.33]
Subtotal (95% CI)	**2604**	**2634**		**49.4 %**	**0.82 [0.50, 1.33]**
Total events: 30 (Systematic), 37 (Opportunistic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.81 (P = 0.42)					
Total (95% CI)	**4562**	**4575**		**100.0 %**	**0.99 [0.71, 1.36]**
Total events: 74 (Systematic), 75 (Opportunistic)					
Heterogeneity: Chi^2 = 1.05, df = 1 (P = 0.31); I^2 =5%					
Test for overall effect: Z = 0.08 (P = 0.94)					
Test for subgroup differences: Chi^2 = 1.05, df = 1 (P = 0.31), I^2 =5%					

Analysis 2.3. Comparison 2 Detection of new cases of atrial fibrillation versus other screening, Outcome 3 Age Subgroups.

Review: Effectiveness of systematic screening for the detection of atrial fibrillation

Comparison: 2 Detection of new cases of atrial fibrillation versus other screening

Outcome: 3 Age Subgroups



ADDITIONAL TABLES

Table 1. Number of new AF cases detected through screening versus routine practice

	Gender		Age Group		Total
	Men	Women	65 - 74	75+	
Systematic Screening	44/1958	30/2604	30/2562	44/2000	74/4562
Opportunistic Screening	38/1941	37/2634	31/2628	44/1947	75/4575

Table 1. Number of new AF cases detected through screening versus routine practice (*Continued*)

Routine Practice	16/1880	31/2633	18/2472	29/2041	47/4513

Data taken from Hobbs 2005 (reported in Fitzmaurice 2007)

Table 2. Uptake of screening

Group	Systematic Screening	Opportunistic Screening
All	53%	46%
Men	57%	49%
Women	50%	41%
Aged 65 - 74	61%	49%
Aged 75+ age	43%	42%

Rates of uptake of screening based on data reported in Hobbs 2005. Rate of uptake of opportunistic screening is based on those who consented to have their pulse taken AND undergo an ECG if an irregular pulse was found.

Table 3. Prevalence data (by gender, age group)

	Men			Women			Total
Group	**65 - 74**	**75 - 84**	**≥ 85**	**65 - 74**	**75 - 84**	**≥ 85**	
Baseline Prevalence							
Control	74/1216 (6.1)	84/703 (11.9)	25/156 (16.0)	44/1378 (3.2)	106/1050 (10.1)	56/420 (13.3)	389/4923 (7.9)
Opportunistic	70/1304 (5.4)	63/650 (9.7)	24/148 (16.2)	48/1448 (3.3)	91/1005 (9.1)	44/375 (11.7)	340/4930 (6.9)
Systematic	69/1318 (5.2)	67/647 (10.4)	15/154 (9.7)	68/1391 (4.9)	70/1022 (6.8)	50/396 (12.6)	339/4928 (6.9)
12 month prevalence							
Control	81/1213 (6.7)	91/699 (13.0)	27/151 (17.9)	55/1377 (4.0)	122/1044 (11.7)	60/418 (14.4)	436/4902 (8.9)
Opportunistic	90/1303 (6.9)	77/647 (11.9)	28/148 (18.9)	59/1443 (4.1)	109/1001 (10.9)	52/373 (13.9)	415/4915 (8.4)

Table 3. Prevalence data (by gender, age group) (*Continued*)

Systematic	90/1312 (6.9)	82/643 (12.8)	23/154 (14.9)	77/1387 (5.6)	88/1012 (8.7)	53/398 (13.5)	413/4906 (8.4)

Data taken from Hobbs 2005 (reported in Fitzmaurice 2007), Figures are number (percentages)

APPENDICES

Appendix 1. Search strategies - RCT

CENTRAL

#1 MeSH descriptor Mass Screening, this term only
#2 (screen*)
#3 MeSH descriptor Diagnosis, this term only
#4 MeSH descriptor Diagnostic Techniques and Procedures, this term only
#5 diagnos*
#6 (identif*)
#7 test*
#8 (prevalence)
#9 (incidence*)
#10 ((systemat* or opportunist* or target* or population or mass) near/2 assess*)
#11 MeSH descriptor Electrocardiography, this term only
#12 MeSH descriptor Electrocardiography, Ambulatory, this term only
#13 (electrocardiogram*)
#14 (electrocardiograph*)
#15 (ecg)
#16 (ekg)
#17 (holter)
#18 (event monitor*)
#19 MeSH descriptor Pulse, this term only
#20 (pulse near/3 test)
#21 (pulse near/3 tests)
#22 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)
#23 MeSH descriptor Atrial Fibrillation, this term only
#24 atrial fibrillation*
#25 (auricular fibrillation*)
#26 (atrium fibrillation*)
#27 (af)
#28 (a-fib)
#29 MeSH descriptor Atrial Flutter, this term only
#30 atrial flutter*
#31 (auricular flutter*)
#32 (#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31)

#33 (#22 AND #32)

MEDLINE

1 Mass Screening/ (72995)
2 screen*.tw. (363165)
3 Diagnosis/ (16201)
4 "Diagnostic Techniques and Procedures"/ (1840)
5 diagnos*.tw. (1357269)
6 identif*.tw. (1481939)
7 test*.tw. (1765452)
8 prevalence.tw. (294233)
9 incidence*.tw. (429563)
10 ((systemat* or opportunist* or target* or population or mass) adj2 assess*).tw. (6956)
11 Electrocardiography/ (154517)
12 Electrocardiography, Ambulatory/ (8229)
13 electrocardiogram*.tw. (29533)
14 electrocardiograph*.tw. (33936)
15 ecg.tw. (40730)
16 ekg.tw. (2117)
17 holter.tw. (7374)
18 event monitor*.tw. (603)
19 or/1-18 (4696543)
20 Atrial Fibrillation/ (28648)
21 atrial fibrillation*.tw. (29152)
22 auricular fibrillation*.tw. (740)
23 atrium fibrillation*.tw. (7)
24 af.tw. (15627)
25 a-fib.tw. (29)
26 Atrial Flutter/ (4663)
27 atrial flutter*.tw. (3879)
28 auricular flutter*.tw. (213)
29 or/20-28 (46988)
30 Pulse/ (15989)
31 (pulse adj3 test).tw. (633)
32 (pulse adj3 tests).tw. (94)
33 19 or 30 or 31 or 32 (4707679)
34 29 and 33 (22662)
35 randomized controlled trial.pt. (321630)
36 controlled clinical trial.pt. (83679)
37 randomized.ab. (226659)
38 placebo.ab. (129223)
39 clinical trials as topic.sh. (158452)
40 randomly.ab. (163835)
41 trial.ti. (97314)
42 35 or 36 or 37 or 38 or 39 or 40 or 41 (746444)
43 exp animals/ not humans.sh. (3683920)
44 42 not 43 (688202)
45 34 and 44 (2438)

EMBASE

1 mass screening/ (45098)

2 screen*.tw. (481715)
3 diagnostic procedure/ (68098)
4 diagnosis/ (991556)
5 diagnos*.tw. (1978130)
6 ((systemat* or opportunist* or target* or population or mass) adj2 (assess* or test*)).tw. (17875)
7 identif*.tw. (1871499)
8 test*.tw. (2435524)
9 prevalence.tw. (385646)
10 incidence*.tw. (621772)
11 electrocardiography/ (126772)
12 electrocardiogram*.tw. (41746)
13 electrocardiograph*.tw. (47763)
14 ecg.tw. (70264)
15 ekg.tw. (3746)
16 holter.tw. (10268)
17 event monitor*.tw. (849)
18 (pulse adj3 test*).tw. (1412)
19 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (6827758)
20 heart atrium fibrillation/ (60141)
21 atrial fibrillation.tw. (44810)
22 auricular fibrillation*.tw. (1890)
23 atrium fibrillation.tw. (31)
24 af.tw. (26527)
25 a-fib.tw. (88)
26 atrial flutter*.tw. (5705)
27 auricular flutter*.tw. (493)
28 or/20-27 (81706)
29 random$.tw. (711679)
30 factorial$.tw. (18953)
31 crossover$.tw. (42881)
32 cross over$.tw. (19756)
33 cross-over$.tw. (19756)
34 placebo$.tw. (176052)
35 (doubl$ adj blind$).tw. (132159)
36 (singl$ adj blind$).tw. (11978)
37 assign$.tw. (199920)
38 allocat$.tw. (67235)
39 volunteer$.tw. (161161)
40 crossover procedure/ (32434)
41 double blind procedure/ (108197)
42 randomized controlled trial/ (301358)
43 single blind procedure/ (14951)
44 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 or 42 or 43 (1197077)
45 (animal/ or nonhuman/) not human/ (4367025)
46 44 not 45 (1055312)
47 19 and 28 and 46 (3896)

Appendix 2. Search strategies - ITS and CBA

MEDLINE

1 intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab. (116218)
2 (pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab. (6563)
3 (hospital$ or patient?).hw. and (study or studies or care or health$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw. (638507)
4 demonstration project?.ti,ab. (1693)
5 (pre-post or "pre test$" or pretest$ or posttest$ or "post test$" or (pre adj5 post)).ti,ab. (48254)
6 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab. (436)
7 trial.ti. or ((study adj3 aim?) or "our study").ab. (456696)
8 (before adj10 (after or during)).ti,ab. (299259)
9 ("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw. (79229)
10 ("time series" adj2 interrupt$).ti,ab,hw. (628)
11 (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or "more than")).ab. (6325)
12 pilot.ti. (29638)
13 Pilot projects/ (69467)
14 (clinical trial or controlled clinical trial or multicenter study).pt. (572420)
15 (multicentre or multicenter or multi-centre or multi-center).ti. (22521)
16 random$.ti,ab. or controlled.ti. (582515)
17 (control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt. (320953)
18 "comment on".cm. or review.ti,pt. or randomized controlled trial.pt. (2511343)
19 review.ti. (198703)
20 (rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti. (1214214)
21 exp animals/ not humans.sh. (3683920)
22 (animal$ not human$).sh,hw. (3590857)
23 *experimental design/ or *pilot study/ or quasi experimental study/ (17650)
24 ("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab. (79229)
25 ("time series" adj2 interrupt$).ti,ab. (628)
26 (or/1-17) not (or/18,20-21) (1712146)
27 (or/1-8,11-12,15-16,23-25) not (or/19,22) (1733779)
28 Mass Screening/ (72995)
29 screen*.tw. (363165)
30 Diagnosis/ (16201)
31 "Diagnostic Techniques and Procedures"/ (1840)
32 diagnos*.tw. (1357269)
33 identif*.tw. (1481939)
34 test*.tw. (1765452)
35 prevalence.tw. (294233)
36 incidence*.tw. (429563)
37 ((systemat* or opportunist* or target* or population or mass) adj2 assess*).tw. (6956)

38 Electrocardiography/ (154517)
39 Electrocardiography, Ambulatory/ (8229)
40 electrocardiogram*.tw. (29533)
41 electrocardiograph*.tw. (33936)
42 ecg.tw. (40730)
43 ekg.tw. (2117)
44 holter.tw. (7374)
45 event monitor*.tw. (603)
46 or/28-45 (4696543)
47 Atrial Fibrillation/ (28648)
48 atrial fibrillation*.tw. (29152)
49 auricular fibrillation*.tw. (740)
50 atrium fibrillation*.tw. (7)
51 af.tw. (15627)
52 a-fib.tw. (29)
53 Atrial Flutter/ (4663)
54 atrial flutter*.tw. (3879)
55 auricular flutter*.tw. (213)
56 or/47-55 (46988)
57 Pulse/ (15989)
58 (pulse adj3 test).tw. (633)
59 (pulse adj3 tests).tw. (94)
60 46 or 57 or 58 or 59 (4707679)
61 56 and 60 (22662)
62 27 and 61 (4762)

EMBASE

1 intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab. (155670)
2 (pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab. (8765)
3 (hospital$ or patient?).hw. and (study or studies or care or health$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw. (1314181)
4 demonstration project?.ti,ab. (2139)
5 (pre-post or "pre test$" or pretest$ or posttest$ or "post test$" or (pre adj5 post)).ti,ab. (70783)
6 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab. (590)
7 trial.ti. or ((study adj3 aim?) or "our study").ab. (636849)
8 (before adj10 (after or during)).ti,ab. (406770)
9 ("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw. (129464)
10 ("time series" adj2 interrupt$).ti,ab,hw. (796)
11 (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or "more than")).ab. (8452)
12 pilot.ti. (39826)
13 Pilot projects/ (52429)
14 (clinical trial or controlled clinical trial or multicenter study).pt. (0)
15 (multicentre or multicenter or multi-centre or multi-center).ti. (30589)
16 random$.ti,ab. or controlled.ti. (762754)

17 (control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt. (504013)
18 "comment on".cm. or review.ti,pt. or randomized controlled trial.pt. (1930931)
19 review.ti. (265182)
20 (rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti. (1527399)
21 exp animals/ not humans.sh. (1681155)
22 (animal$ not human$).sh,hw. (3642616)
23 *experimental design/ or *pilot study/ or quasi experimental study/ (4322)
24 ("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab. (111602)
25 ("time series" adj2 interrupt$).ti,ab. (796)
26 (or/1-17) not (or/18,20-21) (2869531)
27 (or/1-8,11-12,15-16,23-25) not (or/19,22) (2707103)
28 mass screening/ (45098)
29 screen*.tw. (481715)
30 diagnostic procedure/ (68098)
31 diagnosis/ (991556)
32 diagnos*.tw. (1978130)
33 ((systemat* or opportunist* or target* or population or mass) adj2 (assess* or test*)).tw. (17875)
34 identif*.tw. (1871499)
35 test*.tw. (2435524)
36 prevalence.tw. (385646)
37 incidence*.tw. (621772)
38 electrocardiography/ (126772)
39 electrocardiogram*.tw. (41746)
40 electrocardiograph*.tw. (47763)
41 ecg.tw. (70264)
42 ekg.tw. (3746)
43 holter.tw. (10268)
44 event monitor*.tw. (849)
45 (pulse adj3 test*).tw. (1412)
46 28 or 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 or 42 or 43 or 44 or 45 (6827758)
47 heart atrium fibrillation/ (60141)
48 atrial fibrillation*.tw. (44880)
49 auricular fibrillation*.tw. (1890)
50 atrium fibrillation*.tw. (31)
51 af.tw. (26527)
52 a-fib.tw. (88)
53 atrial flutter*.tw. (5705)
54 auricular flutter*.tw. (493)
55 or/47-54 (81720)
56 27 and 46 and 55 (10898)

Appendix 3. Searching other resources

Source	Search Terms
ACC	"atrial fibrillation"
Australia New Zealand Clinical Trials Registry	
Brazilian Clinical Trials Registry	
Chinese Clinical Trials Registry	
Clinical Trials Registry India	
Clinical Trials Registry of the University Medical Center Freiburg	
ClinicalTrials.gov	
EHRA	
EU Clinical Trials Register	
European Stroke Conference	
Eurostroke	
German Clinical Trials Register	
Iranian Registry of Controlled Trials	
ISRCTN Registry	
Japanese NIPH Clinical Trials	
Korean Clinical Research Information Service	
Nederlands Trial Register	
Pan African Clinical Trials Registry	
Sri Lanka Clinical Trials Registry	
Stroke Trials Directory	
UMIN-CTR (Japan)	

(*Continued*)

CINAHL	"atrial fibrillation" and "screening" [abstract]

CONTRIBUTIONS OF AUTHORS

All review authors have contributed to the production of this systematic review. PM wrote the protocol with input from MF, CT, MR and SS. The search strategy was developed by PM, with input from the Cochrane Heart Group Trials Search Coordinator (TSC). Study selection was performed by PM, MF and CT. Risk of bias assessment, data extraction and analysis of the data were carried out by PM and CT. SS and MR provided clinical and methodological guidance and advised on the interpretation of the results. PM wrote the review, with contributions from all authors to the final revision.

DECLARATIONS OF INTEREST

No conflicts of interest are reported.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Health Research Board, Ireland.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol included DARE and ISI Web Of Science with conference proceedings in the list of databases that were to be searched. Given the high volume of results returned from MEDLINE, EMBASE and CENTRAL, these two databases were not included in the search.

INDEX TERMS

Medical Subject Headings (MeSH)

*Asymptomatic Diseases; Atrial Fibrillation [*diagnosis]; Electrocardiography; Mass Screening [*methods]; Palpation [methods]; Pulse [methods]; Randomized Controlled Trials as Topic

MeSH check words

Aged; Female; Humans; Male