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[Intervention Review]

Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation

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ABSTRACT

Background

Current guidelines recommend oral anticoagulation therapy for patients with atrial fibrillation (AF) with one or more risk factors for stroke; however, anticoagulation control (time in therapeutic range (TTR)) with vitamin K antagonists (VKAs) is dependent on many factors. Educational and behavioural interventions may impact patients' ability to maintain their international normalised ratio (INR) control. This is an updated version of the original review first published in 2013.

Objectives

To evaluate the effects of educational and behavioural interventions for oral anticoagulation therapy (OAT) on TTR in patients with AF.

Search methods

We updated searches from the previous review by searching the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) in *The Cochrane Library* (January 2016, Issue 1), MEDLINE Ovid (1949 to February week 1 2016), EMBASE Classic + EMBASE Ovid (1980 to Week 7 2016), PsycINFO Ovid (1806 to Week 1 February 2016) and CINAHL Plus with Full Text EBSCO (1937 to 16/02/2016). We applied no language restrictions.

Selection criteria

We included randomised controlled trials evaluating the effect of any educational and behavioural intervention compared with usual care, no intervention, or intervention in combination with other self-management techniques among adults with AF who were eligible for, or currently receiving, OAT.

Data collection and analysis

Two of the review authors independently selected studies and extracted data. Risk of bias was assessed using the Cochrane 'Risk of bias' tool. We included outcome data on TTR, decision conflict (patient's uncertainty in making health-related decisions), percentage of INRs in the therapeutic range, major bleeding, stroke and thromboembolic events, patient knowledge, patient satisfaction, quality of life (QoL), beliefs about medication, illness perceptions, and anxiety and depression. We pooled data for three outcomes - TTR,

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anxiety and depression, and decision conflict - and reported mean differences (MD). Where insufficient data were present to conduct a meta-analysis, we reported effect sizes and confidence intervals (CI) from the included studies. We evaluated the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Main results

Eleven trials with a total of 2246 AF patients (ranging from 14 to 712 by study) were included within the review. Studies included education, decision aids, and self-monitoring plus education interventions. The effect of self-monitoring plus education on TTR was uncertain compared with usual care (MD 6.31, 95% CI -5.63 to 18.25, I^2 = 0%, 2 trials, 69 participants, very low-quality evidence). We found small but positive effects of education on anxiety (MD -0.62, 95% CI -1.21 to -0.04, I^2 = 0%, 2 trials, 587 participants, low-quality evidence) and depression (MD -0.74, 95% CI -1.34 to -0.14, I^2 = 0%, 2 trials, 587 participants, low-quality evidence) compared with usual care. The effect of decision aids on decision conflict favoured usual care (MD -0.1, 95% CI -0.17 to -0.02, I^2 = 0%, 2 trials, 721 participants, low-quality evidence).

Authors' conclusions

This review demonstrates that there is insufficient evidence to draw definitive conclusions regarding the impact of educational or behavioural interventions on TTR in AF patients receiving OAT. Thus, more trials are needed to examine the impact of interventions on anticoagulation control in AF patients and the mechanisms by which they are successful. It is also important to explore the psychological implications for patients suffering from this long-term chronic condition.

PLAIN LANGUAGE SUMMARY

Educational and behavioural interventions to increase the time in the therapeutic range for patients with atrial fibrillation on anticoagulant therapy

Review question

We reviewed the evidence about the effects of educational and behavioural interventions in patients with atrial fibrillation who are taking oral anticoagulant medication.

Background

Atrial fibrillation is characterised by an irregular heartbeat and places people at greater risk of forming blood clots and having a stroke. To reduce stroke risk, medication that 'thins the blood' is used, known as oral anticoagulants. For patients taking warfarin, regular patient monitoring assesses the time it takes for blood to clot, known as the international normalised ratio (INR), to ensure that the target therapeutic range of 2.0 to 3.0 is maintained. This is often difficult to achieve due to the many factors that can affect INR control such as alcohol intake, other medications, and food.

Educational and behavioural interventions may play an important role in improving the ability of people with atrial fibrillation to maintain their INR control, by increasing patient knowledge and understanding.

Study characteristics

This is an update of the original review first published in 2013. We searched scientific databases in February 2016 and found 11 randomised clinical trials including 2246 adults with atrial fibrillation who were taking oral anticoagulant medication. The trials we found compared education, decision aids, and self-monitoring plus education to usual care, over any length of time.

Key results

Few studies had comparable groups and data. There was uncertainty about the effect of self-monitoring plus education on the percentage of time the INR was within the therapeutic range because the proportion or time in the therapeutic range was similar between individuals who received self-monitoring plus education and those who did not. There were small and positive effects on anxiety and depression in individuals who received education compared to those who received usual care. There were small and negative effects on decision conflict in individuals who received decision aids compared to those who received usual care.

Quality of the evidence

The evidence should be interpreted with caution as the quality of the evidence ranged from very low to low across different outcomes because of the limitations of individual studies. It is likely that further high-quality trials may affect these reported results.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Education, self-monitoring plus education, and decision aids compared to usual care for oral anticoagulant therapy in patients with atrial fibrillation

Patient or population: oral anticoagulant therapy in patients with atrial fibrillation
Setting: hospital, anticoagulation clinic, general physician practice, or research clinic
Intervention: education, self-monitoring plus education, or decision aid as noted
Comparison: usual care

Outcomes	Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
		Risk with usual care	Risk with Intervention				
Percentage of time within the therapeutic range	Self-monitoring plus education	The mean time in therapeutic INR range was 0	MD 6.31 higher (5.63 lower to 18.25 higher)	Not estimable	69 (2 RCTs)	⊕○○○ VERY LOW [123]	Indirect comparison as self-monitoring was compared to placebo and self-management was compared to placebo, but self-monitoring and self-management were not directly compared
HADS anxiety	Education	The mean HADS anxiety was 0	MD 0.62 lower (1.21 lower to 0.04 lower)	Not estimable	587 (2 RCTs)	⊕⊕○○ LOW [23]	
HADS depression	Education	The mean HADS depression was 0	MD 0.74 lower (1.34 lower to 0.14 lower)	Not estimable	587 (2 RCTs)	⊕⊕○○ LOW [23]	
Decision conflict	Decision aid	The mean decision conflict was 0	MD 0.1 lower (0.17 lower to 0.02 lower)	Not estimable	721 (2 RCTs)	⊕⊕○○ LOW [24]	

*The risk in the intervention group (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; **INR:** international normalised ratio; **MD:** mean difference; **RCT:** randomised controlled trial; **HADS:** Hospital Anxiety and Depression Scale

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded due to study limitations including small study bias (all patients had to be eligible for self-management of oral anticoagulation and therefore may not be representative of all AF patients requiring oral anticoagulation)
[2]Downgraded due to attrition bias
[3]Downgraded due to selection bias
[4]Downgraded due to performance bias

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BACKGROUND

Description of the condition

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice (Kirchhof 2016). The lifetime risk of developing AF is approximately one in four among people aged 40 years or older (Lloyd-Jones 2004; McManus 2012). The incidence and prevalence of AF is rising (Chugh 2014; Colilla 2013; Krijthe 2013).The prevalence of AF dramatically increases with age, rising from 0.5% at 40 to 50 years of age to 5% to 15% at 80 years (Chugh 2014; Colilla 2013; Heeringa 2006; Krijthe 2013; Lane 2017; Lloyd-Jones 2004; Miyasaka 2006), with the prevalence being slightly higher in men than in women (Lloyd-Jones 2004; McManus 2012). One US population-based study (N = 4618) found the age- and sex-adjusted incidence of AF per 1000 person-years was 3.04 (95% CI 2.78 to 3.31) in 1980, increasing to 3.68 (95% CI 3.42 to 3.95) in 2000, amounting to a relative increase of 12.6% (Miyasaka 2006). Similar findings in the European Rotterdam Study (N = 6806) found that the overall prevalence of AF was 5.5% to 6.0% in men and 5.1% in women (Heeringa 2006). Recent analyses of the Clinical Practice Research Datalink in the UK demonstrate a constant yearly rise in the prevalence of AF nationally, increasing from 700,000 patients in 2010 to a projected prevalence of between 1.3 million and 1.8 million patients by 2060 (Lane 2017). AF is associated with a five-fold greater risk of stroke and thromboembolism (Wolf 1991), and the incidence of stroke attributable to AF also increases with age (Lip 2006). AF-related stroke is likely to be more severe than non-AF related stroke (Sheikh 2015; Wolf 1991). When including hospital admissions, treatment costs, and long-term nursing home care, AF accounts for 1% of the total UK healthcare expenditure (Sheikh 2015). Given the increasing incidence and prevalence of AF, these figures are likely to rise.

Patients with an increased risk of stroke (as determined by stroke risk stratification models) should receive long-term oral anticoagulant therapy (OAT): either vitamin K antagonists (VKA) such as warfarin, or non-vitamin K antagonist oral anticoagulants (NOAC) such as apixaban, dabigatran, edoxaban, or rivaroxaban, unless contraindicated. In a meta-analysis, dose-adjusted OAT, resulting in international normalized ratio (INR) values in the range of 2.0 to 3.0, significantly reduced the risk of ischaemic stroke or thromboembolism in patients with non-valvular AF by 39% (95% CI 22% to 52%) and 64% (95% CI 41% to 62%), respectively, compared with either aspirin or placebo (Hart 2007). Whilst OAT dramatically reduces stroke risk, the therapeutic range of the INR is narrow and must be maintained. This can be problematic, with INRs greater than 3.0 increasing the risk of major and minor bleeding and INRs less than 2.0 increasing the risk of thromboembolism (Lip 2006). Regular INR monitoring is essential and patients need to carefully adhere to dietary and lifestyle restrictions (Ansell 2004). A retrospective analysis of OAT in the UK demonstrated that only patients with the greatest INR control increased their time to stroke occurrence, with only patients spending over 71% of their time in the target therapeutic range (TTR) benefiting (Morgan 2009). In practice, 51% of patients at high risk of stroke ($CHADS_2$ score 2 or more) remained outside of the target therapeutic range for at least 50% of the time (Morgan 2009). Further, a post hoc analysis of patients enrolled in the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE), which randomised AF patients with one additional stroke risk factor to receive clopidogrel 75 mg/day plus aspirin (75 to 100 mg/day recommended dose) or OAT, found that patients with a TTR less than 58% gained no benefit from OAT. The INR must be within the therapeutic range for at least 58% of the time to confer benefit in terms of stroke risk reduction (Connolly 2008). Thus, maintenance of INR is a major concern for both AF patients and healthcare professionals. Furthermore, whilst interventions targeting this patient group ultimately aim to reduce the risk of stroke, patients' TTR is a good short-term indicator of whether the patients will experience adverse events in the long-term, thus presenting a useful trial endpoint.

The inherent difficulties associated with VKAs (narrow therapeutic range; drug, alcohol, and food interactions; regular blood tests) have led to the development of NOACs, which have sought to overcome these problems by providing an efficacious and safe alternative treatment that does not require regular monitoring. Several NOACs are now available (apixaban, dabigatran, edoxaban, and rivaroxaban) and all are non-inferior to warfarin for the prevention of stroke and systemic embolism, with similar (for dabigatran 150 mg twice daily and rivaroxaban) or better safety profiles (dabigatran 110 mg twice daily, apixaban, and edoxaban) and a significant reduction in intracranial haemorrhage for all NOACs (Connolly 2009; Giugliano 2013; Granger 2011; Patel 2011). The use of NOACs may shift the focus of interventions for this patient group, but VKAs (i.e. warfarin) are still widely used in AF patients and it is important to investigate ways in which we can improve the outcomes of patients still taking VKAs and whether the principles used for interventions with this group are also relevant for those taking NOACs.

Given that AF is a chronic condition that places patients at increased risk of mortality and morbidity - particularly from stroke - and often requires life-long treatment, including chronic OAT, the educational materials and the support given to patients when they are first prescribed OAT are crucial for the maintenance of their treatment regimens.

Description of the intervention

Attempts to support behaviour change can take numerous forms. At the individual level they almost always fall into the category of 'education or communication' and may use one or more behaviour change techniques (Michie 2011; NICE 2007). While some interventions are designed to target regimen simplicity or access to

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testing, education is vital to enable patient uptake and adherence (to medication, treatment regimen, and lifestyle changes). Indeed, patient education for OAT has attempted to influence behaviour by improving knowledge, attitudes, and practices that are necessary to improve health outcomes (Wofford 2008). Yet very few studies define their intervention components in a standardised way, despite novel guidelines that give explicit guidance on how to do so (Michie 2011).

In recent years increased attention has been paid to the classification of behaviour change techniques to aid the development and design of interventions. The behaviour change taxonomy describes 93 distinct techniques that can be applied to understanding a range of health-related behaviours. The taxonomy was validated using obesity and tobacco use as examples, but can be applied to a range of health behaviours including adherence. Defining an intervention using these techniques at the development stage could influence the success of the intervention (Michie 2009; Michie 2013).

Techniques used in delivering patient education cover a wide spectrum, including the use of booklets and videos as media to transmit information either alone or in addition to self-management interventions (such as INR self-monitoring) and interventions that use decision aids (Khan 2004; Man-Son-Hing 1999). Patient knowledge surrounding OAT varies with age, with elderly patients (> 75 years) demonstrating poorer knowledge (Tang 2003). In one study, less than half of participants were able to name even one specific benefit, risk, or lifestyle change associated with warfarin (Coehlo-Dantas 2004). In several cases, spouses were more knowledgeable than the patients and appeared to play a vital role in monitoring the individuals' treatment regimens (Coehlo-Dantas 2004). Therefore, educational interventions for this patient group may prove to be particularly beneficial.

Other interventions focus on behavioural and practical aspects of lifestyle change and treatment. Behavioural interventions aim to modify patients' behaviour towards treatment and symptoms (NICE 2007). Interventions that use these principles to promote change include cognitive behavioural therapy (CBT), motivational interviewing, and heart rate variability biofeedback. CBT is a goal-oriented, systematic procedure which aims to solve problems concerning dysfunctional emotions, behaviours, and cognitions and to promote positive attitude, self efficacy, and planning. However, with any complex intervention it is difficult to determine which component has influenced the behavioural outcome, as researchers often do not define the active components of the intervention and interventions vary in duration and levels of support. Clearly it is important for trials to be explicit about the content and delivery of their interventions and to choose appropriate evaluative tools in order to examine how and why their interventions are successful, by using an applied behaviour change model (Kok 2016; Michie 2011).

How the intervention might work

Interventions for patients with AF who receive OAT should ultimately aim to improve clinical outcomes, primarily reducing the prevalence of stroke and mortality. However, in the short-term we can aim to increase patients' TTR by focusing on factors that affect treatment adherence. Many factors can affect INR control, such as drug-drug interactions and variable dietary vitamin K intake (Holbrook 2005), but with adequate knowledge surrounding treatment and lifestyle factors, interventions should aim to encourage behaviour change.

It has been suggested that several factors influence adherence (Horne 2013; Lane 2015; Thrall 2004), and these factors are either intentional or unintentional. Intentional non-adherence can occur when patients make a decision not to take their treatment as a result of their personal motivations or beliefs, or both (Horne 2013). Unintentional non-adherence refers to an individual's skills or ability to take his or her medications (for example problems with remembering to take tablets). Poor INR control could result from both unintentional and intentional non-adherence (Horne 2013). Where patients' knowledge of their condition and their OAT is limited, this may impact on their practical ability to manage treatment (unintentional) and their perceptions surrounding treatment necessity (intentional). Indeed several studies have demonstrated that patients have poor knowledge of AF and its treatment (Lane 2006; Lip 2002; Nadar 2003; Tang 2003).

There is evidence that patient knowledge correlates significantly with TTR (Tang 2003), with more knowledgeable patients having a better TTR. Thus if education can demonstrate an improvement in TTR, it could have important clinical benefits (that is the reduction of adverse events such as stroke and major bleeding). Decision aids are informative interventions designed to help people make specific choices surrounding their medications, and they may also increase patient knowledge. These interventions aim to reduce decision conflict, which refers to the patient's uncertainty in making health-related decisions and the factors relating to that uncertainty, which may subsequently impact on treatment uptake and adherence.

Intentional non-adherence may be more difficult to target and interventions need to focus on inaccurate perceptions of medications. The common sense model (Horne 1999) suggests that patients hold beliefs about the necessity of their prescribed medication (Specific-Necessity) and concerns about prescribed medication based on beliefs about the danger of dependence and long-term toxicity as well as the disruptive effects of the medication (Specific-Concerns). The model also describes general beliefs about medication, assessing beliefs that medicines are addictive and harmful (General-Harm) and that medicines are over-prescribed by doctors (General-Overuse). These beliefs, and the way in which patients balance their concern about medications, have been widely used in predicting medication adherence in a variety of chronic conditions including rheumatoid arthritis (Neame 2005), asthma (Jessop 2003), type II diabetes (Farmer 2006), and

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depression (Aikens 2005).

A comparison of beliefs about medications between adherent, unintentional non-adherent, and intentionally non-adherent patients found significant differences in medication-related beliefs in patients with a range of chronic illnesses after being newly prescribed medication for the last 10 days (Clifford 2008). Compared with adherers, intentional non-adherers had significantly lower scores on the necessity sub-scale of the Beliefs about Medication Questionnaire (P = 0.012), higher scores on the concerns sub scale (P = 0.008), and lower scores on the necessity-concerns differential (P = 0.001). There were no significant differences between adherers and unintentional non-adherers (Clifford 2008). Evidently, whilst unintentional non-adherers may benefit from memory aids (that is reminders, tablet dosettes), intentional non-adherers may need to address both their perceptions of their medication and misinformation, which may be achieved by increasing patient education surrounding their treatment. Intentional non-adherers appear to doubt their personal need for their medication and have concerns about taking it when compared to adherers.

More recent models critique the categories of 'intentional' and 'unintentional', as there is overlap between the categories. For example, whilst forgetting is unintentional it may be influenced by intentional or motivational factors (McHorney 2011). The capability, opportunity and motivation (COM-B) model of behaviour was developed in order to choose interventions that are most likely to be effective and specific for the individual behaviour (Jackson 2014). This model hypothesises that the interaction between an individual's capability, opportunity and motivation (COM) cause the performance of behaviour (B). Thus the model provides explanations for why patients do not adhere to treatment regimens. Patient's capability includes their psychological and physical capacity to engage in necessary thought processes including disease comprehension, cognitive functioning (e.g. memory capacity) and executive function (e.g. capacity to plan). A complex medication regimen, such as with a VKA (i.e. warfarin), might be beyond the psychological planning capabilities of some patients. Motivation is defined as brain processes that energise and direct behaviour such as the perception of illness, beliefs about treatment, self-efficacy and outcome expectancies. Some evidence suggests that individuals with complex regimens for several conditions choose to take the medication that offers the most symptom relief, or is treating the most feared condition (Nunes 2009). Opportunity is defined as the physical opportunity provided by the environment including cost, access, physical characteristics of the medicine, regimen complexity, social support and the relationship with the healthcare provider (HCP). For VKAs this may include the barriers to regular INR testing, and the social support required to attend appointments and make and maintain lifestyle changes. This model provides a more precise method of defining the causes of non-adherence, going beyond the dichotomies of intentional and unintentional, and thus may prove to be a useful model when developing interventions with this patient group.

Research suggests that interventions with the greatest likelihood of success are theoretically underpinned, and precisely describe the behavioural change techniques employed to address the needs of target patient group (Michie 2009; Michie 2013).

Why it is important to do this review

AF is a condition that is increasing in prevalence (Chugh 2014; Lane 2017; Miyasaka 2006) and requires treatment with OAT to reduce associated stroke risk. However, patients on VKAs need to maintain a narrow therapeutic INR range, which may be difficult to achieve in practice (Morgan 2009). Patients need sufficient information to make informed choices and actively participate in the management of their own treatment (Lane 2015; Thrall 2004). Patient education aims to influence patient behaviour and improve knowledge, attitudes, and practices that are necessary to improve health outcomes (Wofford 2008), but the efficacy of patient interventions designed to improve AF patient adherence to OAT is not clear. By increasing patient knowledge and understanding surrounding AF and OAT we may reduce the prevalence of intentional and unintentional non-adherence, and increase patient motivation to adhere, in addition to providing patients with the tools to improve their planning and capability to incorporate the regimen required with VKA therapy into their lifestyle (Jackson 2014), which may subsequently increase TTR. TTR is important and has been shown to be a predictor of thromboembolic or haemorrhagic complications, although it is a surrogate for the hard endpoints such as reductions in mortality and stroke that OAT is aimed at achieving. Many factors influence TTR, including adherence to medication and lifestyle factors (e.g., alcohol intake, diet and other medications), however, TTR does give an indication as to whether patients are adhering to the regimen required for VKA therapy, which should translate into a reduction in stroke and major bleeding events. We updated our previous review (Clarkesmith 2013) to evaluate the value of educational and behavioural interventions for patients with AF who were currently prescribed VKA (mainly warfarin), including the impact on TTR and secondary outcomes such as decision conflict, patient knowledge, and quality of life.

OBJECTIVES

To evaluate the effects on TTR of educational and behavioural interventions for OAT in patients with AF.

METHODS

Criteria for considering studies for this review

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Types of studies

We included randomised controlled trials (RCTs) of educational or behavioural interventions with any length of follow-up and in any language.

Types of participants

Adults (aged 18 years or older) with AF, categorised according to the European Society of Cardiology (ESC) guidelines (Kirchhof 2016), including:

- newly diagnosed AF;
- paroxysmal AF, defined as episodes that usually terminate spontaneously (usually in less than 48 hours), but may last for up to seven days;
- persistent AF, characterised by an episode lasting more than seven days or requiring termination via cardioversion;
- long-standing persistent AF, where AF has been present for > one year (i.e. permanent AF) but where a rhythm control strategy is adopted;
- permanent AF, where AF has been continuous for more than one year and accepted as the 'normal' heart rhythm by the patient and the physician (hence no rhythm control adopted).

AF was diagnosed and documented by electrocardiogram (12-lead or Holter monitoring). Patients that were eligible for, or currently receiving, OAT were considered for inclusion in this review. We also included studies which included AF patients with other medical conditions in this review. The studies were RCTs comparing at least one intervention with a control group, and including patients with AF as either the study population or a specified subgroup. We only included studies where patients were grouped per indication, that is for patients taking oral anticoagulants for AF, deep vein thrombosis (DVT) or pulmonary embolism (PE), valve replacements, etc, we only included AF patient data within the analysis.

Types of interventions

We considered all types of educational and behavioural interventions given to AF patients who were taking OAT for this systematic review. Educational interventions included those that delivered patient information, such as:

- educational booklets;
- videos as media to transmit additional information;
- self-management interventions (such as INR self-monitoring) that also educated patients;
- decision aids;
- talking interventions.

Behavioural interventions included techniques that attempted to modify patients' behaviour towards treatment and symptoms, such as:

- cognitive behavioural therapy (CBT);
- self-monitoring or management interventions that include significant educational components;
- motivational interviewing;
- heart rate variability biofeedback.

Interventions could target adults on the individual level or as a group. The intervention may have taken place in the emergency department, a hospital, the home, or in the community and could have been delivered by a nurse, pharmacist, educator, health or medical practitioner, or a multidisciplinary team associated with the hospital or referred to by the hospital. The intervention could have been undertaken at any time point from diagnosis of AF or initiation of OAT (that is not only newly diagnosed AF patients or those newly referred for anticoagulant therapy). We only considered trials where the comparison groups were usual care, no intervention, or the intervention in combination with other self-management techniques. We defined usual care as standard anticoagulation clinic practice, where patients attended routine INR checks (defined as usual care by the author). We included any length of follow-up. We have endeavoured to ensure that our review is clearly distinct from the Garcia-Alamino 2010 review, which exclusively evaluated the effects of self-monitoring or self-management of OAT compared to standard monitoring. In particular, we have only included self-monitoring interventions where they include a clear and distinct educational component (in addition to training on the use of the self-monitoring device); this should include topics in addition to self-testing, such as risk information, lifestyle changes, and information pertaining to their condition.

Types of outcome measures

Primary outcomes

The primary outcome measure was TTR, as defined by Rosendaal 1993 (INR 2.0 to 3.0).

Secondary outcomes

The secondary outcomes were:

- major bleeding (defined as bleeds that result in death, are life threatening, cause chronic sequelae, or consume major healthcare resources) and minor bleeding (Schulman 2004);
- stroke and thromboembolic events;
- increased knowledge with regard to AF and anticoagulation therapy;
- patient satisfaction;
- acceptability of the anticoagulant therapy;
- quality of life; psychological well-being (anxiety and depression);
- changes in perception towards AF and INR control;
- changes in the patients' illness beliefs and illness representations;

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- self-reported adherence to treatment and a change in the patients' beliefs about medications;
- economic costs of the intervention (cost-effectiveness);
- decision conflict*.

*We included decision conflict as a secondary outcome in the final analysis. Whilst not specified as an outcome of interest in the original protocol, it was highlighted as a common secondary outcome measure in three of the studies included in the final review. For this reason, we decided to include these data within the results. Decision conflict measures (1) healthcare consumers' uncertainty in making a health-related decision; (2) the factors contributing to the uncertainty; and (3) healthcare consumers' perceived effective decision making.

These outcomes were quantified using validated or non-validated questionnaires, ratings, or scales.

Search methods for identification of studies

Electronic searches

We updated searches from the previous review (Clarkesmith 2013) by searching the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) in *The Cochrane Library* (January 2016, Issue 1 of 12), MEDLINE Ovid (1949 to February week 1 2016), EMBASE Classic + EMBASE Ovid (1980 to Week 7 2016), PsycINFO Ovid (1806 to Week 1 February 2016) and CINAHL Plus with Full Text EBSCO (1937 to 16/02/2016). See Appendix 1 for the search strategies.

Searching other resources

We handsearched abstract books from national and international cardiology, psychology, and psychiatry conferences to include meetings relating to AF and meetings that discussed the development of educational and behaviour change interventions, including:

- European Society of Cardiology;
- American College of Cardiology;
- American Heart Association;
- Society for Behavioural Medicine and the Division of Health Psychology Conference;
- European Health Psychology Conference;
- Royal College of Psychiatrists Annual Meeting.

We also searched dissertation abstracts (UMI ProQuest Digital Dissertations) and reference lists of all relevant papers to identify other potentially relevant articles.

We did not apply any language restrictions to the searches.

Data collection and analysis

Selection of studies

Two authors (Clarkesmith and Lane) independently scrutinised the titles found from the search and decided on inclusion or exclusion. For the 2016 update, two authors (Clarkesmith and Khaing) independently reviewed the abstracts and papers for inclusion and exclusion. We used Cohen's kappa statistic to assess agreement between the two authors on the selection of articles for inclusion. At the first review stage (June 2010), the kappa coefficient was 98.4%. Following the updated search in 2012, the kappa coefficient was 95%. For the current update, the kappa coefficient was 85%. Where disagreements arose, the full-text article was accessed to determine whether the study met the inclusion and exclusion criteria and a third author reviewed the studies (Lane). The authors discussed the article and agreement was reached by consensus.

Data extraction and management

Two review authors independently extracted the data. For each trial, the following data were extracted (where available) using a specially designed data extraction form: participants (sample size, age, sex, ethnicity, marital status, type of AF); type of anticoagulation therapy (VKA, i.e.,warfarin, other); type and duration of the interventions (intervention versus usual care or no intervention, other combinations); primary (TTR) and secondary outcomes (increase in knowledge with regard to AF and anticoagulation therapy, decision conflict, time within the therapeutic INR range, patient satisfaction, acceptability of the anticoagulant therapy, quality of life, changes in perception towards AF and INR control, changes in the patients' illness beliefs and illness representations, changes in the patients' beliefs about medications, self-reported adherence, psychological well-being); length of follow-up; statistical methods employed; the effect size and its precision. Studies were included in this review if they reported any of the primary or secondary outcomes of interest, regardless of whether the original study's primary or secondary outcomes corresponded with the review's primary or secondary outcomes. For example, if a study reported TTR as a secondary outcome, we included the TTR in this review as part of the primary outcome.

Assessment of risk of bias in included studies

Two review authors (Clarkesmith and Lane) independently assessed the risk of bias of each trial in accordance with guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We determined the risk of bias using the Cochrane 'Risk of bias' tool. We assessed the following criteria.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias) and of outcome assessors (detection bias).

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- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other sources of bias.

We judged each criteria as low risk, high risk, or unclear risk.

Sequence generation

- Low risk, if the allocation sequence was generated using techniques such as a random number table; a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; or cluster randomisation.
- High risk, if the allocation sequence was generated using techniques such as odd or even date of birth; date (or day) of admission; hospital or clinic record number.
- Unclear risk, if there was insufficient information about the sequence generation process to permit judgement.

Allocation concealment

- Low risk, if the allocation concealment used methods such as central allocation (including telephone, web-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered opaque, sealed envelopes.
- High risk, if the participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque, or not sequentially numbered); alternation or rotation; date of birth; case record number.
- Unclear risk, if the method of concealment was not described or not described in sufficient detail to allow a definite judgement (e.g. if the use of assignment envelopes was described but it remained unclear whether envelopes were sequentially numbered, opaque, and sealed).

Where the method of allocation was unclear, we contacted study authors to provide further details.

Blinding

- Low risk, if there was no blinding but the review authors judged that the outcome and the outcome measurement were not likely to be influenced by lack of blinding; if blinding of participants and key study personnel was ensured and it was unlikely that the blinding could have been broken; if either participants or some key study personnel were not blinded but outcome assessment was blinded and the non-blinding of others was unlikely to introduce bias.
- High risk, if there was no blinding or incomplete blinding and the outcome or outcome measurement was likely to be influenced by lack of blinding; if blinding of key study participants and personnel was attempted but it was likely that the blinding could have been broken; if either participants or some key study personnel were not blinded and the non-blinding of others was likely to introduce bias.
- Unclear risk, if there was insufficient information to permit judgement or the study did not address this outcome (e.g. where the blinding was described only as double-blind without any other details).

Incomplete data assessment (loss of participants, for example with withdrawals, dropouts, protocol deviations)

- Low risk, if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome; missing outcome data were balanced in numbers across intervention groups with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; missing data were imputed using appropriate methods; for cluster randomised trials, an error made in statistical analysis when the analysis does not take account of the unit of allocation.
    - In some studies, the unit of allocation is not a person but is instead a group of people. Sometimes the data from these studies are analysed as if people had been allocated individually. Using individuals as the unit of analysis when groups of people are allocated can result in overly narrow confidence intervals. Thus, where included in meta-analysis, it can result in studies receiving more weight than is appropriate and this must be accounted for.
- High risk, if the reasons for missing outcome data were likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was enough to introduce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes was enough to introduce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
- Unclear risk, if there was insufficient reporting of attrition or exclusions to permit judgement (e.g. numbers randomised were not stated, no reasons for missing data were provided), or the study did not address this.

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Selective outcome reporting

- Low risk, if the study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that were of interest in the review were reported in the pre-specified way; the study protocol was not available, but it was clear that the published reports included all expected outcomes including those that were pre-specified.
- High risk, if not all of the study's pre-specified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (e.g. sub scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the study report failed to include results for a key outcome that would be expected to have been reported for such a study.
- Unclear risk, if there was insufficient information to permit judgement.

Other sources of bias

- Low risk, if the study appeared to be free of other sources of bias.
- High risk, if there was at least one important risk of bias (e.g. the study had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal stopping rule); had extreme baseline imbalance; had been claimed to be fraudulent; had some other problem).
- Unclear, if there was either insufficient information to assess whether an important risk of bias existed or if there was insufficient rationale or evidence that an identified problem would not introduce bias.

Measures of treatment effect

We undertook statistical analyses as follows. For continuous variables (for example changes in illness perception questionnaire or changes in TTR), we calculated the mean difference (MD) with 95% confidence interval (CI). Had we been able to pool any dichotomous variables, we would have calculated odds ratios (OR) with 95% CI.

Dealing with missing data

Where the article indicated inclusion of AF patients, but data were not included by subgroup, we contacted the authors of the included studies to gather AF-specific data. We also contacted authors where there was insufficient detail on the demographic data for AF patients or the content of the intervention. We received responses and additional data from several authors (Beyth 2000; Christensen 2007; Clarkesmith 2013; Gadisseur 2003; Hendriks 2013; Polek 2012; Thomson 2007; Vormfelde 2014). For fifteen studies the authors could not be contacted (Al-Meshal 2013; Lakshmi 2013; Moore 2013; Sawicki 1999; Stone 1989; Verret 2012; Watzke 2000) or did not respond to e-mail or written requests for unpublished data (Barcellona 2006; Chan 2006; Gardiner 2006; Jank 2009; Menendez-Jandula 2005; Ryan 2009; Siebenhofer 2007; Yildirim 2015). For two studies, we successfully contacted the authors but the data were unavailable (Machtinger 2007; Moss 2014). If authors responded with data that were incomplete, we contacted them again for further details.

Assessment of heterogeneity

We assessed heterogeneity of studies included in the meta-analysis using the I^2 statistic and Chi^2 test for heterogeneity. Data were considered heterogenous if the P value was less than or equal to 0.10, for which random-effect models were used. Fixed-effect models were used where the P value was greater than 0.10.

Assessment of reporting biases

There were not enough studies in this review to test for reporting bias, thus we discuss the findings narratively. However, future revisions will test for bias using a funnel plot based on the data for the primary outcome of TTR. Asymmetry of the funnel plot will be taken as an indication of publication bias. Other causes of asymmetry of the funnel plot will also be explored, such as clinical heterogeneity between studies (for example, different control event rates) or methodological heterogeneity between studies (for example, failure to conceal allocation). We summarised information on blinding during both the collection and analysis of study data in a narrative review; this information informed the risk of bias assessments. We also summarised the completeness of the reported data, including any concerns over the exclusion of participants or excessive dropouts. We also reported concerns over the selective reporting of outcomes, time points, or subgroups.

Data synthesis

We combined results of individual studies within a narrative review. Where possible and appropriate, we used meta-analysis to statistically combine results. We included TTR data if directly reported using the Rosendaal method of calculation (Rosendaal 1993), or where available from personal communication with the authors. For the analysis we used Review Manager to calculate the summary statistics (RevMan 2014). We examined heterogeneity using the Chi^2 and the I^2 statistics (Higgins 2011). We evaluated the quality of evidence using the GRADE approach (Higgins 2011), and we employed GRADE profiler to to create a 'Summary of findings' table GRADEpro 2015.

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Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses looking at the type of intervention (educational alone, behavioural alone, and a combination of education and behavioural versus usual care). Future revisions may also examine frequency (one session versus multiple sessions) and duration (less than six months versus more than six months) of the intervention, length of time on OAT, men versus women, individual versus group interventions, and age of participant groups, dependant upon the availability of such data in the included study reports.

Sensitivity analysis

There were insufficient studies to carry out sensitivity analyses. However, future revisions of the review may employ sensitivity analyses to examine factors that may lead to differences between the results of individual trials: poor quality versus good quality trials.

RESULTS

Description of studies

Results of the search

The search retrieved 1560 de-duplicated articles from all sources. Of these, we excluded 1451 by assessing the titles and abstracts. We obtained 109 full-text articles for consideration.

We excluded 86 articles based on review of the full-texts. Of these, we included one new study as an ongoing trial. Of the three ongoing trials included in the previous version of this review (Clarkesmith 2013), we included two as studies in this review and excluded one based on subsequent information in the published results suggesting the trial was not randomised (further details are given in the Excluded studies section). We included a total of 20 articles reporting on 11 studies in this review (Figure 1). A further three articles relating to the included studies were found subsequent to the searches and are included as references.

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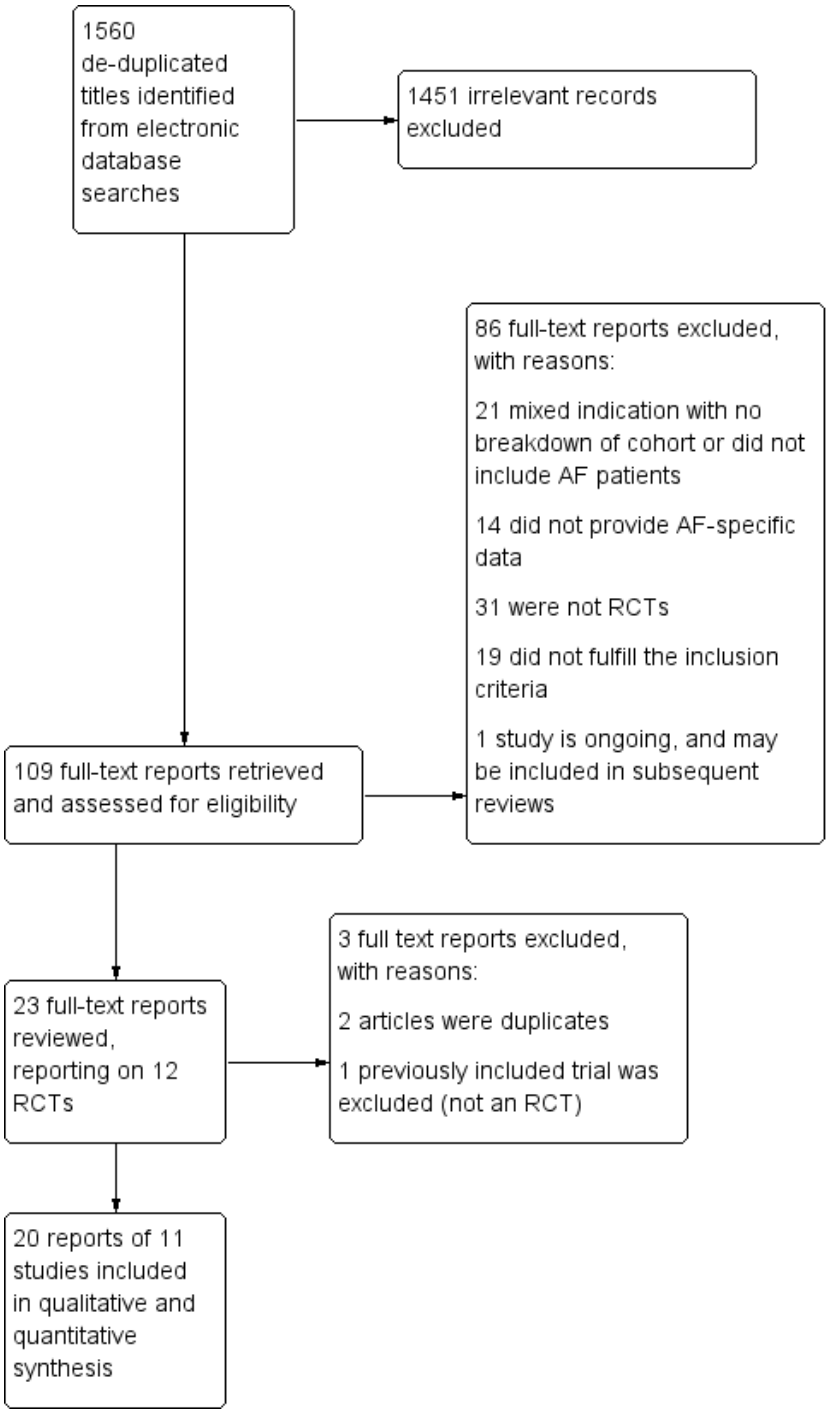
Figure 1. PRIMSA flow chart of included studies.



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Included studies

Thirteen articles reporting on eight studies were included in the original Cochrane review (Beyth 2000; Christensen 2007; Gadisseur 2003; Man-Son-Hing 1999; McAlister 2005; Polek 2012; Thomson 2007; Voller 2005). For this update we have identified a further ten articles reporting on three studies (Clarkesmith 2013; Hendriks 2013; Vormfelde 2014). Two of these studies were included in the previous review (Clarkesmith 2013) as ongoing trials and now have published results (Clarkesmith 2013; Vormfelde 2014). Features of the interventions are included in the Characteristics of included studies. See the PRISMA flow chart for the inclusion process (Figure 1).

Methods

The 11 included studies were randomised controlled trials. Six of the studies specifically recruited AF patients (Clarkesmith 2013; Hendriks 2013; Man-Son-Hing 1999; McAlister 2005; Thomson 2007; Voller 2005). A further five 'mixed' trials recruited patients with a range of indications for OAT (for example AF, venous thromboembolism, cardiovascular disease, heart valve prosthesis, peripheral vascular disease, or myocardial infarction) and the authors provided unpublished data on the AF patients (Beyth 2000; Christensen 2007; Gadisseur 2003; Polek 2012; Vormfelde 2014). Two trials were cluster randomised studies (McAlister 2005; Vormfelde 2014), and one used a Zelen design (Gadisseur 2003).

Participants

The total sample size of 2246 AF patients, including published and unpublished data, varied by trial from 14 to 712 participants (Polek 2012 (unpublished), and Hendriks 2013, respectively). The mean age of the trial participants, from studies that reported age, ranged from 59 to 75 years. One trial did not provide any demographic information for their AF patients (Gadisseur 2003).

Patients were included if they had AF (Clarkesmith 2013; Hendriks 2013; McAlister 2005; Thomson 2007; Voller 2005); had ECG documented AF (Clarkesmith 2013; Hendriks 2013); were receiving intravenous heparin (Beyth 2000); were aged 18 years or over (Christensen 2007; Clarkesmith 2013; Hendriks 2013; McAlister 2005), 60 years or over (Thomson 2007), 65 years or over (Beyth 2000), or 18 to 75 years (Gadisseur 2003); planned to start warfarin (Beyth 2000; Gadisseur 2003; Polek 2012; Thomson 2007); had been taking warfarin for any length of time (Thomson 2007; Vormfelde 2014), greater than three months (Gadisseur 2003), less than 3 months (Clarkesmith 2013), or greater than eight months (Christensen 2007); were accessible via telephone (Polek 2012); and had German language skills (Vormfelde 2014).

Patients were excluded if they had been treated with warfarin at any time in the previous six months (Beyth 2000); had contraindications for warfarin (Clarkesmith 2013); previously received warfarin (Clarkesmith 2013); were admitted from a nursing home (Beyth 2000; Polek 2012); were enrolled in another clinical trial (Beyth 2000; Voller 2005); were too ill to give consent (Beyth 2000) or did not speak English (Beyth 2000; Clarkesmith 2013; McAlister 2005; Polek 2012; Thomson 2007); had previously used self-management for INR (Christensen 2007); had antiphospholipid syndrome (Gadisseur 2003), a life threatening illness (Gadisseur 2003), life expectancy less than or equal to one year (Clarkesmith 2013; Gadisseur 2003; McAlister 2005), cognitive impairment (Clarkesmith 2013; Gadisseur 2003; McAlister 2005; Polek 2012; Thomson 2007), physical limitations making successful participation impossible (Gadisseur 2003), or poor hearing or eyesight (Voller 2005); had experienced a major haemorrhage in a previous trial (Man-Son-Hing 1999); were taking warfarin for another condition (McAlister 2005; Thomson 2007; Voller 2005); were scheduled for cardioversion (McAlister 2005; Thomson 2007) or cardiac surgery (Vormfelde 2014); had a history of psychotic disorder (Polek 2012), previous stroke or transient ischaemic attack (TIA; Thomson 2007), valvular heart disease (Clarkesmith 2013), unstable or uncontrolled hypertension (Vormfelde 2014), unstable heart failure (Vormfelde 2014), untreated hyperthyroidsim (Vormfelde 2014), current or forseen pacemaker (Vormfelde 2014), internal cardioverter defibrillator (Vormfelde 2014), or alcohol or other addiction (Voller 2005).

Types of studies

Of the eleven studies that were identified, five compared education with usual care (Clarkesmith 2013; Gadisseur 2003; Hendriks 2013; Polek 2012) or usual care with an educational booklet (Vormfelde 2014), four compared self-monitoring plus education with usual care (Beyth 2000; Christensen 2007; Gadisseur 2003; Voller 2005), and one also included a self-management group (Gadisseur 2003). A further three trials focused on the use of a decision support aid versus usual care (Man-Son-Hing 1999; McAlister 2005) or a 'guideline evidence' comparison group (Thomson 2007).

Types of interventions

Interventions were either one to one (Beyth 2000; Hendriks 2013; McAlister 2005; Polek 2012; Vormfelde 2014) or group training sessions (Gadisseur 2003; Voller 2005), or both (Clarkesmith 2013). Three of the trials did not explicitly specify a group or

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individual intervention type (Christensen 2007; Man-Son-Hing 1999; Thomson 2007).

All of the interventions included an educational element, usually consisting of a description of the consequences of minor or major stroke and major haemorrhage, the blood monitoring required for VKA (i.e. warfarin), and the probability of stroke and major haemorrhage for patients taking a VKA. Most interventions also included information regarding the lifestyle factors influencing VKA control and provided written educational materials or a booklet. Two of the interventions also included a video component (Clarkesmith 2013; Vormfelde 2014). Self-monitoring interventions included training on the use of INR monitoring devices (Beyth 2000; Christensen 2007; Gadisseur 2003; Voller 2005).

Decision aid interventions offered more detailed information on the risks of bleeding and thromboembolism (Man-Son-Hing 1999; McAlister 2005; Thomson 2007). All three trials using a decision support aid employed pictograms to depict the risk of stroke and bleeding on either placebo, aspirin, or warfarin; two utilised paper-based charts (Man-Son-Hing 1999; McAlister 2005) and the third used a computerised version (Thomson 2007). The decision aid was presented and patients were asked to select which treatment they would prefer on the basis of the risk information presented in the pictogram (probability trade-off technique). For example, the consequences of a minor stroke, a major stroke, and minor and major bleeding were described along with the probability of those events occurring whilst taking different treatment options. This gave patients the opportunity to make informed decisions (Man-Son-Hing 1999); in this trial patients completed a worksheet which summarised the information following use of the decision aid.

Duration of the intervention

The duration of the educational training element of the interventions varied. Seven trials reported a one-off consultation of 30 to 60 minutes (Beyth 2000; Clarkesmith 2013; Thomson 2007; Vormfelde 2014) or three to four sessions each lasting 30 to 120 minutes (Gadisseur 2003; Hendriks 2013; Voller 2005). The other four trials did not specify how long the intervention lasted or the number of sessions (Christensen 2007; Man-Son-Hing 1999 McAlister 2005; Polek 2012).

Intervention facilitator

Two studies did not specify the type of facilitator (Christensen 2007; Voller 2005). Of those that did, facilitators included a lay educator (Beyth 2000); a physician, pharmacist, or healthcare professional (Gadisseur 2003; McAlister 2005; Polek 2012); a computerised audio tool (Man-Son-Hing 1999; Thomson 2007); a trainee health psychologist (Clarkesmith 2013); a practice nurse (Vormfelde 2014); and a nurse specialist (Hendriks 2013).

Country

The geographical settings of the studies were: Denmark (Christensen 2007), the Netherlands (Gadisseur 2003; Hendriks 2013), Germany (Voller 2005; Vormfelde 2014), USA (Beyth 2000; Man-Son-Hing 1999; Polek 2012), Canada (McAlister 2005), and the UK (Thomson 2007; Clarkesmith 2013).

Setting for the intervention

Most of the interventions were conducted in a hospital or anticoagulation clinic setting (Beyth 2000; Christensen 2007; Clarkesmith 2013; Gadisseur 2003; Hendriks 2013; Man-Son-Hing 1999; Polek 2012). Two of the trials took place in general practitioner (GP) practices (McAlister 2005; Vormfelde 2014), with another taking place in a research clinic with patients from general practices (Thomson 2007). One of the trials did not describe the intervention setting (Voller 2005).

Follow-up

Assessment of the impact of the intervention on outcomes was at three (Polek 2012), six (Beyth 2000; Christensen 2007; Clarkesmith 2013; Gadisseur 2003; Man-Son-Hing 1999; Vormfelde 2014), and 12 months (Clarkesmith 2013; Hendriks 2013; McAlister 2005; Thomson 2007).

Funding

Four of the trials declared some funding input by drug companies (Clarkesmith 2013; Gadisseur 2003; Man-Son-Hing 1999; Voller 2005).

Excluded studies

We excluded 86 studies for the following reasons.

1. Twenty-one studies were excluded for not providing a breakdown of a mixed indication cohort per indication (Al-Meshal 2013; McCahon 2011; Moore 2013; Nilsson 2011; Suriano 2014; Vadher 1996; Vadher 1997; Verret 2012), or not including AF patients (Baker 1991; Bump 1977; Claes 2005; Claes 2006; Cordasco 2009; Cromheecke 2000; Cromheecke 2001; Fitzmaurice 2005; Holbrook 2007; Landefeld 1992; Mazor 2007; Pernod 2008; Waterman 2001).

2. Fourteen studies did not provide AF-specific findings, and attempts to obtain the specific data from the authors were unsuccessful. For twelve of these studies the authors could not be contacted (Lakshmi 2013; Stone 1989; Sawicki 1999; Watzke 2000), or did not respond to e-mail or written requests for unpublished data (Barcellona 2006; Chan 2006; Gardiner 2006; Jank 2009; Menendez-Jandula 2005; Ryan 2009; Siebenhofer 2007; Yildirim 2015). For two studies, the author was successfully contacted but the data were unavailable (Machtinger 2007; Moss 2014).

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3. Thirty-one studies were not RCTs (Armstrong 2011; Bajorek 2005; Blaise 2009; Bloomfield 2011; Burns 2009; Castelino 2010; Corbella 2009; Davis 2005; Duran-Parrondo 2011; Fraenkel 2011; Hasan 2011; Heidbuchel 2015; Krause 2010; Leger 2004; Megden 1999; Morin 2015; Nedaz 2002; Polzien 2007; Qvist 2016; Reverdin 2011; Saokaew 2010; Satger 2009; Sawicki 2003; Stafford 2011; Taylor 1997; Tuiskula 2011; Turc-Dessertine 2005; Winans 2010; Witt 2005; Woodend 2005; Wurster 2006).
4. Nineteen studies did not fulfil other predefined inclusion criteria. Seven did not include an educational or behavioural intervention (Field 2010; Fitzmaurice 1996; Fitzmaurice 2000; Gouin-Thibault 2010; Matchar 2005; Trivalle 2010; Waterman 2001 b). Five studies provided education on self-monitoring alone with no additional education on AF and the risks and benefits of OAT (Christensen 2011; Dolor 2010; Grunau 2011; Matchar 2010; Sunderji 2005). None of the studies were excluded for including participants <18 years of age. Five studies did not report any of the pre-specified outcomes (Batty 2001; Jackson 2004; O'Sullivan 2016; PRISM Study group 2003; Peng 2014). One of the studies did not randomise their usual care group (Khan 2004). One of the studies did not have a separate control group; patients acted as their own historical control (Bereznicki 2013).
5. One study eligible for inclusion is an ongoing trial and the results are not yet available (Siebenhofer 2012).
Two studies that were excluded from a previous version of this review as they were ongoing trials are now included (Clarkesmith 2013; Vormfelde 2014), and one has been excluded as it was not an RCT (Stafford 2011).

Risk of bias in included studies

The risk of bias for each of the included studies is summarised in Figure 2 and Figure 3. Individual domains are summarized below, with detailed information for each in the Characteristics of included studies tables.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

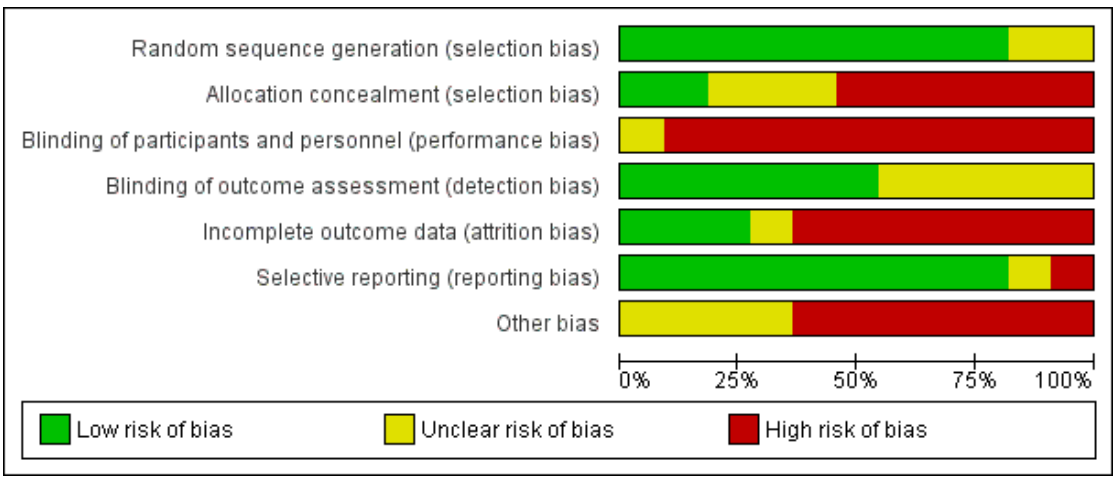

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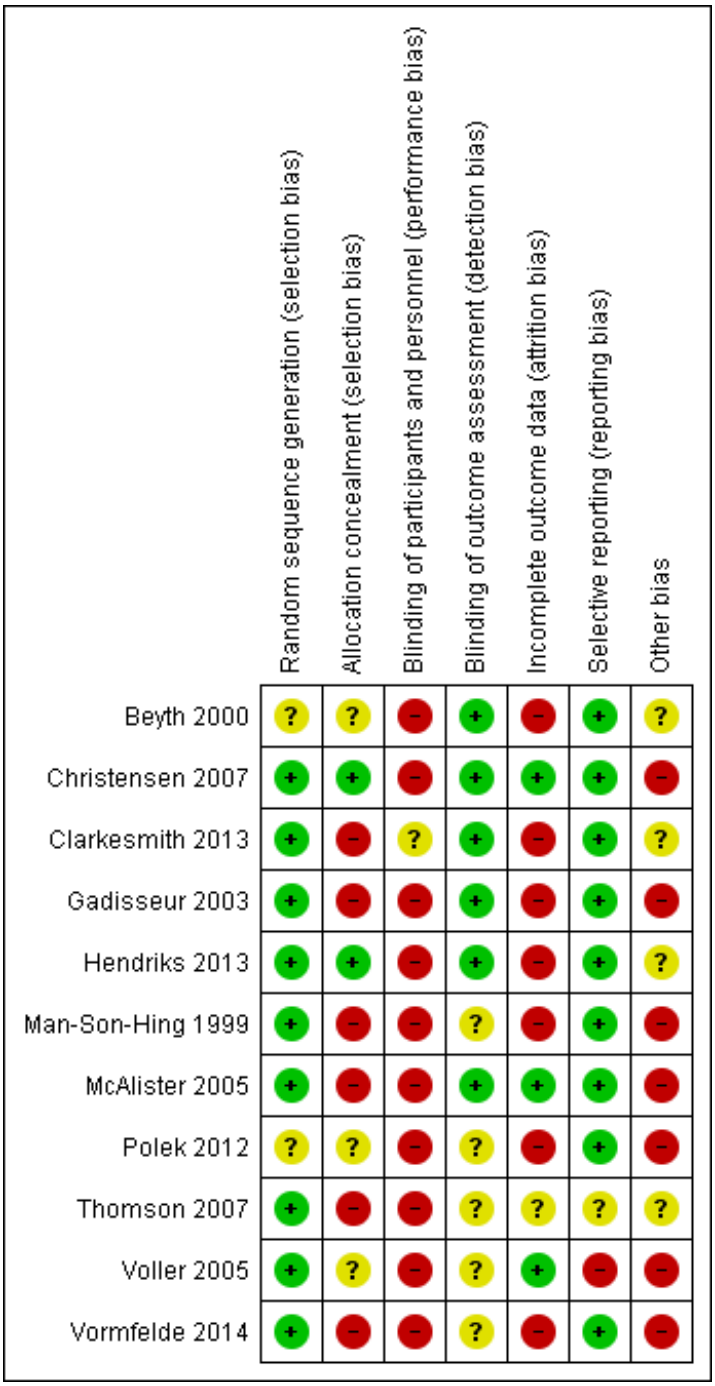
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Nine of the included trials provided information about adequate sequence generation. For the majority of trials this consisted of randomisation to the intervention or usual care according to: a computer-generated sequence using block randomisation (Christensen 2007; Clarkesmith 2013; Man-Son-Hing 1999; McAlister 2005; Thomson 2007); one-to one randomisation (Hendriks 2013); a random numbers table (Voller 2005); or a two-step partial-Zelen design (Gadisseur 2003). The other two trials did not provide details of sequence generation (Beyth 2000; Polek 2012).

Two studies used cluster randomisation at the level of the family physician (McAlister 2005; Vormfelde 2014). All eligible patients within any one physician's practice were allocated to the intervention or usual care practices. This process avoided contamination that may have occurred if the same physician delivering the intervention also delivered usual care.

All of the studies reported the number of eligible participants; however, for the mixed cohort trials it was difficult to retrospectively assess which of the screened patients had AF. Of those trials specifically recruiting AF patients, the percentage of eligible patients randomised ranged from 15% to 94% (Clarkesmith 2013 and Hendriks 2013, respectively). In the mixed indication cohort trials this percentage ranged from 18% to 95% (Gadisseur 2003 and Christensen 2007, respectively). Thus, some of the trials were more representative than others. Those trials that included less than 50% of the eligible participants were at risk of selection bias (Clarkesmith 2013; Gadisseur 2003; Man-Son-Hing 1999; McAlister 2005; Thomson 2007; Vormfelde 2014), whereby patient characteristics may affect the study outcomes. For example, those patients that participated may have been more motivated or willing to participate. One study did not report how many participants were eligible for the study (Voller 2005).

Blinding

Blinding patients to the intervention they were receiving was not possible with these types of interventions, nor was it possible to blind the intervention facilitator to which arm the patients were in. This inevitably raises the risk of bias for all studies. Experimenter bias could have occurred in these trials, whereby the individuals delivering the intervention and usual care could behave differently towards a group inadvertently, affecting the study outcome. There was one exception to this (Clarkesmith 2013), where all INR monitoring (primary outcome) was undertaken at an independent anticoagulation clinic where the employees were not aware of the treatment allocation. However, blinding of the outcome assessors (the data analysts or researchers) regarding to which intervention arm the patient was assigned was possible, in principle, and was undertaken in six trials (Beyth 2000; Clarkesmith 2013; Christensen 2007; Gadisseur 2003; Hendriks 2013; McAlister 2005). Five trials did not state whether their outcome assessor was blinded to the group to which the patients were randomised (Man-Son-Hing 1999; Polek 2012; Thomson 2007; Voller 2005; Vormfelde 2014) or indeed whether the individual delivering the intervention also carried out the analysis, which inevitably increases the risk of bias.

Incomplete outcome data

The percentage of patients completing the final follow-up with data available for all outcomes ranged from 55% to 100% (Clarkesmith 2013 and Voller 2005, respectively). Attrition greater than 20% was considered to indicate high risk of bias. Attrition was greater for questionnaire follow-ups than clinical follow-ups (such as those trials reporting TTR or cardiovascular death as their primary outcome). If attrition is related to any feature of the study design or instrumentation, or leads to bias between groups, this will increase the risk of bias. Some of the self-monitoring and decision aid studies reported participants as lost to follow-up due to an inability to perform the tests or to understand the decision aid. Other reasons included discontinuing warfarin, moving away from the area, death, illness, and hospitalisation. Where patients were unable to use the intervention, this could lead to a high risk of bias, compared to a more 'capable' sample.

Selective reporting

Five of the studies published a protocol paper (Clarkesmith 2013; Hendriks 2013; McAlister 2005; Voller 2005; Vormfelde 2014). McAlister and Hendriks reported on all but one of the pre-specified outcomes (patient satisfaction). Two studies reported on all of their pre-specified outcomes (Voller 2005; Vormfelde 2014), although one trial was ended early due to insufficient participant numbers to power the primary outcome (Voller 2005), Clarkesmith reported on all pre-specified outcomes other than cost-effectiveness (Clarkesmith 2013). A further six studies did not publish protocol papers (Beyth 2000; Christensen 2007; Gadisseur 2003; Man-Son-Hing 1999; Polek 2012; Thomson 2007), but reported on all the outcomes specified within their method section.

Other potential sources of bias

Over the course of the study, participant characteristics may change. With increasing age the participants in these studies were likely to have suffered from additional comorbidities and started taking new medications. These trial designs cannot control for the impact of concomitant medications or the additional burden of new medication regimens across the study period, thus this may have increased the risk of bias for all trials. Four trials required

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patients to be able to undertake self-monitoring and/or self-management of INR (Beyth 2000; Christensen 2007; Gadisseur 2003; Voller 2005), and therefore these patients may not be representative of all patients requiring OAT; however, in one study all patients were aged 65 years or older so the results of this study may be more generalisable to the mainly elderly AF population (Beyth 2000). In two trials there was a difference at baseline between groups in terms of the antithrombotic therapy that patients were receiving (those already receiving warfarin and those not) which could have affected patients' ability to make decisions about treatment (one of the outcomes was decision conflict; McAlister 2005; Thomson 2007). In one study, improvement in knowledge was dependent on the GP practice where the patient education was delivered, most probably due to differences in the patient-nurse discussions after the video presentation (Vormfelde 2014). In one trial, there was the possibility of contamination between the intervention and usual care groups, as physicians could have provided similar information contained within the educational booklet to the usual care group during routine clinic visits (Man-Son-Hing 1999). In two trials, the type of intervention (comprehensive nurse-led; Hendriks 2013) or the intervention facilitator (health psychologist; Clarkesmith 2013), could suggest that the results may not be applicable outside these settings.

Effects of interventions

See: **Summary of findings for the main comparison** Education, self-monitoring plus education, and decision aids compared to usual care for oral anticoagulant therapy in patients with atrial fibrillation

Various methods of measuring outcomes were employed; this was the main obstacle when comparing study findings. This was further complicated by the different time points at which measurements were taken, depending on the length of the trial. Further, the included studies differed in type (behavioural and decision aids) and in their comparator group. Where data were comparable - that is, using the same measurement tool and type of intervention - we requested AF-specific data if it was not provided in the published article. We report key results in Summary of findings for the main comparison, and summarize them below by outcome and intervention.

Primary outcomes

TTR

The TTR (INR of 2.0 to 3.0) was reported by five trials (Beyth 2000; Christensen 2007; Clarkesmith 2013; Gadisseur 2003; Vormfelde 2014) as outlined by the Rosendaal method (Rosendaal 1993). One trial reported the TTR in days (Voller 2005). Three trials reported other indicators of INR control: percentage of in-range INRs (McAlister 2005; Voller 2005), and combined INR and complications outcomes (Christensen 2007). Of those studies reporting TTR, all tested self-monitoring plus education or education only interventions (Beyth 2000; Christensen 2007; Gadisseur 2003; Vormfelde 2014), but only two published AF-specific data (Voller 2005; Clarkesmith 2013) and one of those trials did not use the Rosendaal method (Voller 2005). Thus, we contacted the remaining trial authors for AF-specific data, which were provided by three of the authors (Christensen 2007; Gadisseur 2003; Vormfelde 2014). We did not request AF-specific data for outcomes that were not comparable; that is, combined INR and complications outcomes (Christensen 2007).

Education intervention

Four of the included trials compared education only and usual care (Clarkesmith 2013; Gadisseur 2003; Polek 2012; Vormfelde 2014). Three of these trials reported TTR (Clarkesmith 2013; Gadisseur 2003; Vormfelde 2014).

Gadisseur 2003 studied a cohort with a mixed indication for OAT and provided additional unpublished data on the AF cohort for the three arms of the trial who received INR self-monitoring training including education: self-management, self-measurement, and routine care in educated patients. They found that the TTR was highest in the educated usual care group (mean 75.0%, SD 18.5%), followed by the self-measurement group (mean 70.3%, SD 18.7%), followed by the educated usual care group (mean 67.1%, SD 26.4%) and lowest in the self-management group (mean 64.7%, SD 18.3%). These groups were not comparable to Vormfelde 2014, as there was no control comparator in Vormfelde 2014 that did not receive education. These groups were also not comparable to Clarkesmith 2013 as the education in Gadisseur 2003 was not AF-specific.

Clarkesmith 2013 studied an AF cohort and found significantly higher TTR in the intervention group (median 76.2%, interquartile range (IQR) 64.1% to 97.3%) than the usual care group (median 71.3%, IQR 51.2% to 84.7%) at six months, but no significant difference between the groups at 12 months (median 76.0%, IQR 60.5% to 85.0% versus median 70.0%, IQR 62.0% to 79.0%, respectively).

Vormfelde 2014 recruited a mixed indication cohort, but provided unpublished AF-specific data. TTR was significantly higher in the intervention group (mean 69%, SD 25.1%) compared to the brochure only group (mean 64%, 28.2%) at 6-months.

Self-monitoring plus education intervention

Four trials examined the impact of self-monitoring plus education (Beyth 2000; Christensen 2007; Gadisseur 2003; Voller 2005).

Christensen 2007 recruited patients with multiple indications for OAT, with only 20 AF patients: 11 receiving self-management plus education and nine in the usual care group. INR control

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was slightly higher in the intervention group (mean 77.3%, SD 11.6%) than in the usual care group (mean 67.9%, SD 23.5%; MD 9.3%, 95% CI -7.5% to 26.2%; not significant).

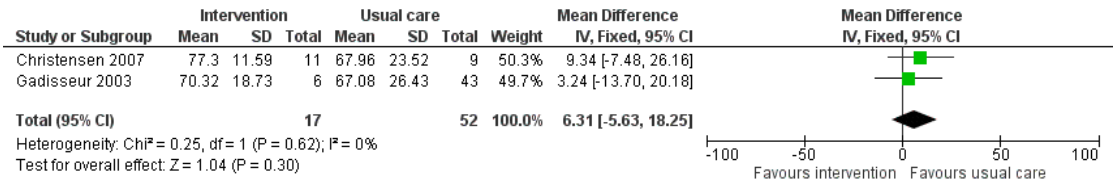
Gadisseur 2003 was also a mixed cohort trial where the authors provided unpublished data on AF patients. TTR in the self-monitoring plus education group (mean 70.3%, SD 18.7%) was slightly higher than in the usual care group (mean 67.1%, SD 26.4%; MD 3.2%, 95% CI -13.7% to 20.2%; not significant).

Beyth 2000 did not provide AF-specific data on TTR outcomes and thus could not be included in these analyses.

Voller 2005 reported cumulative percentage of time in INR rather than TTR by the Rosendaal method. TTR in the self-monitoring group (mean 67.8%, SD 17.6%) was significantly higher than in the usual care group (mean 58.5%, SD 19.8%).

The fixed-effects pooled analysis of the two studies reporting TTR using the Rosendaal method of calculation demonstrated that self-monitoring plus education did not significantly improve TTR when compared to usual care (MD 6.3%, 95% CI -5.63% to 18.25%; Christensen 2007; Gadisseur 2003; Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: self-monitoring plus education versus usual care on time in therapeutic INR range.



Education versus self-monitoring plus education intervention

One trial compared self-monitoring plus education with education only (Gadisseur 2003).

Gadisseur 2003 provided unpublished data on AF patients that suggested the TTR was slightly higher in the education only group (mean 75.0%, SD 18.5%) than in the self-monitoring plus education group (mean 70.3%, SD 18.7%).

Decision aid intervention

One trial reported the percentage of INRs in range (McAlister 2005).

Percentage of INRs within the therapeutic range differed from TTR as the outcome was not calculated using the Rosendaal method (Rosendaal 1993). McAlister 2005 found that INR control deteriorated in the usual care arm over time (INRs were between 2.0 and 3.0 on 66% of the days at three months versus 70% of the days at baseline), while INR control improved in the intervention arm (INRs were between 2.0 and 3.0 on 72% of the days at three months versus 65% at baseline). The between group difference was statistically significant (P = 0.02). By 12 months, INR control in both arms had regressed back to baseline levels. However, the usual care and intervention groups were not well matched at baseline.

Secondary outcomes

Major and minor bleeding, stroke, and thromboembolic events

Two studies reported major bleeding, stroke, and thromboembolic events (Beyth 2000; Clarkesmith 2013), and one provided unpublished AF-specific data (Beyth 2000). None of the studies reported on minor bleeding. Two studies reported mortality (Beyth 2000; Hendriks 2013), one specified cardiovascular death (Hendriks 2013), but the other did not specify if death was due to a cardiovascular cause (Beyth 2000). Three studies reported the number of thromboembolic or haemorrhagic complications (Clarkesmith 2013; Voller 2005; Vormfelde 2014), with one reporting specifically on those requiring medical treatment (Voller 2005).

Self-monitoring plus education intervention

One study provided unpublished AF data on major bleeding, stroke, and thromboembolic events (Beyth 2000). This study found the number of cases of major bleeding in the self-monitoring plus education group (n = 1, 1.8% of total AF cohort) was similar to the number of cases in the usual care group (n = 2, 3.7% of total AF cohort). There were also very few cases of stroke and

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thromboembolic events in the self-monitoring plus education (n = 1, 1.8% of total AF cohort) and usual care (n = 2, 3.7% of total AF cohort) groups (Beyth 2000). Voller 2005 measured thromboembolic and bleeding events. Two severe haemorrhages occurred in one patient in the self-monitoring group, and one thromboembolic event occurred in the usual care group.

Increased knowledge with regard to AF and anticoagulation therapy

Seven trials reported on patient knowledge (Clarkesmith 2013; Hendriks 2013; Man-Son-Hing 1999; McAlister 2005; Polek 2012; Thomson 2007; Vormfelde 2014). Five trials assessed knowledge before and after the intervention (Clarkesmith 2013; Hendriks 2013; Man-Son-Hing 1999; Thomson 2007; Vormfelde 2014), and two only tested knowledge after the intervention (McAlister 2005; Polek 2012). All trials used different measurement tools for assessing knowledge.

Education intervention

Four trials reported on patient knowledge (Clarkesmith 2013; Hendriks 2013; Polek 2012; Vormfelde 2014). All trials used different knowledge questionnaires and therefore data could not be pooled.

Two trials reported on mixed indication cohorts (Polek 2012; Vormfelde 2014). One trial provided unpublished AF data on knowledge outcomes (Polek 2012). They found slightly higher knowledge scores in the intervention group (mean 11.2, SD 1.6) than the usual care group (mean 10.1, SD 1.7) at the 12-week follow-up. However, the number of AF patients in this mixed cohort was too small to draw definitive conclusions. Vormfelde 2014 did not provide AF-specific data on patient knowledge to include in this review.

Hendriks 2013 found a greater improvement in knowledge between baseline and 12-month follow-up in the intervention group (mean 7.21, SD 2.30 versus mean 8.23, SD 2.16, respectively) than the usual care group (mean 6.91, SD 2.54 versus mean 7.66, SD 2.09, respectively). Between-group differences were significant at follow-up (P = 0.028).

Clarkesmith 2013 found no significant differences in knowledge between baseline and six-month follow-up for the intervention or usual care groups (median (IQR) score at baseline 6 (5 to 7) in the intervention group versus 6 (4 to 7) in the usual care group; at six-month follow-up 7 (6 to 7) versus 7 (4 to 7), respectively).

Decision aid intervention

Two trials reported on patient knowledge (Man-Son-Hing 1999; Thomson 2007).

Thomson 2007 used an extension of the decision conflict scale (O'Connor 1995), and found that although knowledge scores after the intervention had improved slightly, by three-month follow-up they had returned to pre-intervention levels. There was no significant difference between the decision aid and guidelines groups at any point.

Man-Son-Hing 1999 used a non-validated scale and demonstrated that patients in the decision aid group had significantly greater knowledge of treatment-related information than those in the usual care group (aspirin-related knowledge MD 15.9, 95% CI 4.6 to 27.2, P < 0.001; warfarin-related knowledge MD 14.9, 95% CI 4.6 to 25.2, P < 0.001).

Patient satisfaction

Four trials included patient satisfaction as a specified outcome (Gadisseur 2003; Hendriks 2013; Man-Son-Hing 1999; McAlister 2005). However, one trial did not report results for this outcome (McAlister 2005).

Education intervention

One education trial reported patient satisfaction; however, the authors did not provide AF-specific data for this outcome (Gadisseur 2003).

Decision aid intervention

One trial using a decision aid intervention reported patient satisfaction as an outcome (Man-Son-Hing 1999). They found that the use of the decision aid did not significantly affect patients' satisfaction with their physician consultations.

QoL: psychological well-being (anxiety and depression)

Three studies reported on QoL as an outcome (Clarkesmith 2013; Gadisseur 2003; Hendriks 2013), using three different measurement tools (Brazier 1992; Badia 2007; Sawicki 1999). One of the trials did not publish AF-specific data for QoL (Gadisseur 2003). Two trials reported anxiety and depression outcomes (Clarkesmith 2013; Hendriks 2013), measured by the Hospital Anxiety and Depression Scale (Zigmond 1983). One study reported on anxiety alone (Thomson 2007), using a different measurement tool (Spielberger 1969).

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Education intervention

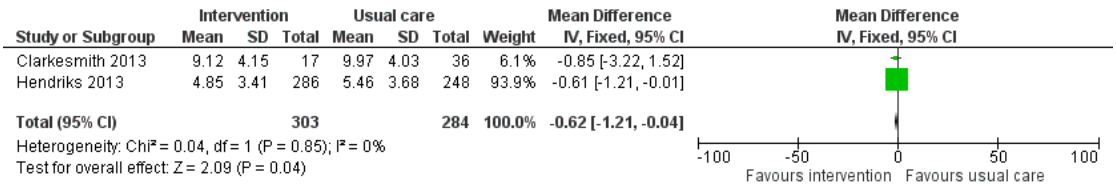
Two trials reported on anxiety (Clarkesmith 2013; Hendriks 2013). Both trials used the Hospital Anxiety and Depression Scale to measure anxiety (Zigmond 1983).

Clarkesmith 2013 provided unpublished scores for anxiety. They found a greater increase in anxiety from baseline to 6 months in the intervention group (mean 6.14, SD 5.13) than the usual care group (mean 3.86, SD 6.36), but these differences were not significant (P = 0.14). There were no significant differences in anxiety between baseline and 12 months in either the intervention (mean 2.41, SD 5.28) or usual care (mean 2.71, SD 5.86) groups (P = 0.86). Between 6 and 12 months there was a slight, but non-significant (P = 0.24), decrease in anxiety in both the intervention (mean -3.00, SD 5.33) and usual care (mean -0.35, SD 5.86) groups.

Hendriks 2013 reported no significant changes in anxiety from baseline (median 5, IQR 3 to 9) to 12 months (median 5, IQR 3 to 8) in the intervention group. In the usual care group there were no significant changes in scores from baseline (median 5, IQR 3 to 9) to 12 months (median 4, IQR 2 to 7). They found no significant differences in anxiety between groups, but a significant increase within both the intervention (median change -1, IQR -3 to 1) and usual care (median change -1, IQR -2 to 1) groups across time (P < 0.001).

The fixed-effects pooled analysis of the two studies reporting anxiety using the Hospital Anxiety and Depression Scale (HADS) demonstrated that education had a small but positive impact on anxiety when compared to usual care (MD -0.62, 95% CI -1.21 to -0.04, P = 0.04; Clarkesmith 2013; Hendriks 2013; Analysis 2.1; Figure 5).

Figure 5. Forest plot of comparison: education versus usual care on HADS anxiety.

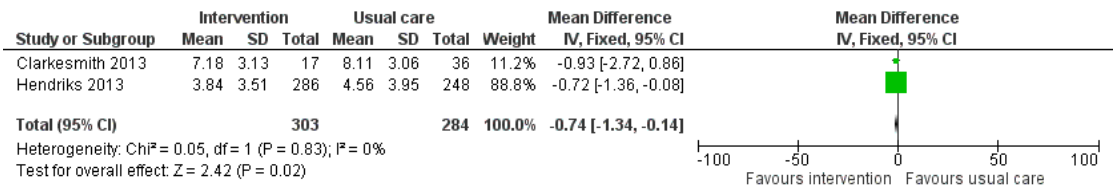


Clarkesmith 2013 provided unpublished data for depression. The found a similar increase in depression from baseline to 6 months for the intervention (mean 4.32, SD 3.20) and usual care (mean 4.00, SD 3.20) groups; these differences were not significant (P = 0.71). The difference in depression was less between baseline and 12 months in both the intervention (mean 2.88, SD 4.1) and usual care (mean 2.88, SD 5.15) groups (P = 1.00). Between 6 and 12 months there was a slight, but non-significant (P = 0.55) decrease in depression in both the intervention (mean -1.73, SD 3.10) and usual care (mean -1.06, SD 2.66) groups.

Hendriks 2013 also provided unpublished data for depression and found no significant change in depression from baseline to 12 months in the intervention (median 4, IQR 1 to 7 versus median 3, IQR 1 to 6) and usual care groups (median 4, IQR 2 to 7 versus median 4, IQR 2 to 7).

The fixed-effects pooled analysis of the two studies reporting depression using the HADS questionnaire demonstrated that education had a small but positive impact on depression when compared to usual care (MD -0.74, 95% CI -1.34 to -0.14, P = 0.02; Clarkesmith 2013; Hendriks 2013; Analysis 2.2; Figure 6).

Figure 6. Forest plot of comparison: education versus usual care on HADS depression.



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Two trials reported on QoL (Clarkesmith 2013; Hendriks 2013). Hendriks and colleagues used the SF-36 questionnaire (Ware 1992), whilst the other used the AF-QoL questionnaire (Badia 2007).

Hendriks 2013 found no significant differences between groups on any of the SF-36 sub-scales. There were significant changes within groups across time for vitality (intervention: P = 0.008; usual care: P < 0.00), physical role (usual care: P = 0.004), bodily pain (usual care: P = 0.002), emotional role (intervention: P = 0.004), and mental health (intervention: P = 0.001).

Clarkesmith 2013 found no significant differences between or within groups on any of the AF-QoL subscales.

Decision aid intervention

Only one trial reported anxiety as an outcome (Thomson 2007). Anxiety fell significantly in both groups pre- to post-clinic, (MD -4.57, 95% CI -6.30 to -2.84), but there was no evidence of a significant difference in anxiety between the two groups (F (1, 95) = 0.001; P = 0.98).

Changes in the patients' illness beliefs and illness representations

One study reported on illness perceptions, and beliefs about medications (Clarkesmith 2013).

Education intervention

One study reported on illness perceptions (Clarkesmith 2013). They found no significant differences between the intervention and usual care groups on any of the sub-scales.

One study reported on beliefs about medication (Clarkesmith 2013). The usual care group scored higher than the intervention group on specific concerns about medication and general harm scales at all time points. There was also a significant difference between groups in the perception of general harm (F (1, 28) = 4.4; P < 0.05) and an interaction between time and group for patients' concerns regarding medication (F (4, 27) = 2.9; P = 0.02). There was a significant interaction between group and time for patients' perceptions of the overuse of medication (F (4, 28) = 2.4, P = 0.04). The usual care group perceived medication as more overused than the intervention group. Scores on the Specific-Necessity sub-scale of the Beliefs about Medicines Questionnaire were similar for both groups, but there were no significant differences across time or between groups.

Economic costs of the intervention (cost-effectiveness)

Two studies measured cost-effectiveness of the intervention (Clarkesmith 2013; Hendriks 2013), but one study did not report on this outcome and did not provide data (Clarkesmith 2013).

Education intervention

Hendriks 2013 found the cost-effectiveness acceptability curve for cost per quality-adjusted life year demonstrated that if willingness to pay is set at EURO20 000, the possibility of nurse-led care being cost-effective is 99% compared with usual care. For cost per life-year a probability of 92.5% is reached at a willingness to pay of EURO20 000.

Decision conflict

Three studies reported on decision conflict (Man-Son-Hing 1999; McAlister 2005; Thomson 2007). One of the studies did not have a usual care arm and therefore was not included in the pooled data analysis (Thomson 2007).

Decision aid intervention

Three studies (Man-Son-Hing 1999; McAlister 2005; Thomson 2007) reported decision conflict, and all used the decision conflict scale (O'Connor 1995).

Man-Son-Hing 1999 found that the usual care arm (mean 1.74, SD 0.5) scored slightly higher on decision conflict than the decision aid arm (mean 1.6, SD 0.4; MD -0.09, 95% CI -0.2 to 0.02).

McAlister 2005 found that the usual care arm (mean 1.7, SD 0.5) scored slightly higher on decision conflict than the decision aid arm (mean 1.6, SD 0.5; MD -0.10, 95% CI -0.19 to -0.01).

Although three studies reported decision conflict as an outcome, only two compared differences in the usual care and decision aid intervention groups (Man-Son-Hing 1999; McAlister 2005). The third compared the decision aid with a guideline comparison group and therefore was not included in the meta-analysis (Thomson 2007). Data from the two trials were pooled and the random-effects analysis favoured usual care in terms of reducing decision conflict (MD -0.10, 95% CI -0.17 to -0.02; Man-Son-Hing 1999; McAlister 2005; Analysis 3.1; Figure 7).

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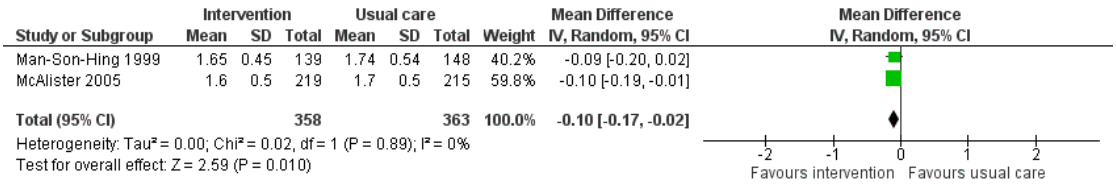
Figure 7. Forest plot of comparison: decision-aid versus usual care on decision conflict.



Other outcomes

None of the studies reported on:

- patient acceptability of anticoagulant therapy;
- changes in perception towards AF and INR control;
- self-reported adherence to treatment

DISCUSSION

Summary of main results

This review found eleven RCTs of behavioural and educational interventions for anticoagulant therapy in patients with AF (Beyth 2000; Christensen 2007; Clarkesmith 2013; Gadisseur 2003; Hendriks 2013; Man-Son-Hing 1999; McAlister 2005; Polek 2012; Thomson 2007; Voller 2005; Vormfelde 2014). Five trials compared education with usual care (Clarkesmith 2013; Gadisseur 2003; Hendriks 2013; Polek 2012; Vormfelde 2014), four compared self-monitoring plus education with usual care (Beyth 2000; Christensen 2007; Gadisseur 2003; Voller 2005), and one trial also compared a self-management group (consisting of self-testing and self-dosing; Gadisseur 2003). Three trials focused on the use of a decision support aid versus usual care (Man-Son-Hing 1999; McAlister 2005) or a comparison group (Thomson 2007). The analyses included a small number of trials with small sample sizes, thus more evidence is needed to draw definitive conclusions.

Education

We have summarised the findings from the education trials in Summary of findings for the main comparison. Two trials comparing education and usual care reported on anxiety and depression (Hendriks 2013; Clarkesmith 2013). Pooled data demonstrated that education had a small but positive impact on anxiety (MD -0.62, 95% CI -1.21 to -0.04, P = 0.04) and depression (MD -0.74, 95% CI -1.34 to -0.14, P = 0.02) when compared to usual care over 12 months (Analysis 2.1; Analysis 2.2; Figure 5; Figure 6). These findings are influenced by the weighting of the trial by Hendriks and colleagues, and the 12 month follow-up data for both trials, as Clarkesmith 2013 found a decline in both anxiety and depression in both groups at the 6 month follow-up. Evidently patients may feel more anxious and depressed in the initial months following diagnosis and treatment commencement.

Self-monitoring plus education versus usual care

We have summarised the findings from the self-monitoring trials in Summary of findings for the main comparison. Two self-monitoring plus education trials reported TTR (Christensen 2007; Gadisseur 2003). Pooled data for the AF patients demonstrated that self-monitoring plus education did not significantly improve TTR when compared to usual care (MD 6.3, 95% CI -5.63 to 18.25; Analysis 1.1; Figure 4). One previous Cochrane Review compared self-management (monitoring and dosing) and self-monitoring (monitoring only) interventions for mixed indication patients taking OAT (Garcia-Alamino 2010). In their pooled data analysis, self-management interventions showed significant reductions in both thromboembolic events (RR 0.50, 95% CI 0.36 to 0.69) and all-cause mortality (RR 0.64, 95% CI 0.46 to 0.89), but self-monitoring did not. The findings from the current review support those by Garcia-Alamino 2010 that in an AF cohort, self-monitoring is no more successful in increasing INR control than usual care.

Decision aids

We have summarised the findings from the decision aid trials in Summary of findings for the main comparison. Decision aid trials favoured usual care over the intervention in minimising decision conflict (MD -0.10, 95% Cl -0.17 to -0.02; Analysis 3.1; Figure 7). The use of a decision aid did not have a significant impact on AF patients' anxiety levels (Thomson 2007) or patient satisfaction (Man-Son-Hing 1999). This suggests that patients that took part in the decision aid trial were uncertain as to which treatment they were going to choose.

Overall completeness and applicability of evidence

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Five of the included trials had mixed indication cohorts (Beyth 2000; Christensen 2007; Gadisseur 2003; Polek 2012; Vormfelde 2014), and 14 further trials were excluded as they did not provide AF-specific data (Barcellona 2006; Chan 2006; Gardiner 2006; Jank 2009; Lakshmi 2013; Machtinger 2007; Menendez-Jandula 2005; Moss 2014; Ryan 2009; Sawicki 2003; Siebenhofer 2007; Stone 1989; Watzke 2000; Yildirim 2015). Recruiting patients with mixed indications for a VKA can be problematic. Patients often have different INR ranges (for example with valve replacements) and each patient group is unique in their lifestyle and treatment recommendations. AF patients are often older (Kannel 1998), prescribed treatment on a long-term basis (NICE 2006), and susceptible to inaccurate beliefs surrounding their illness (Steed 2010) due to their symptoms being irregular and often unrecognised (Fuster 2006). Thus, it is essential that interventions are disease specific, yet only three of the included trials specifically mentioned educating the patients about AF (Clarkesmith 2013; Hendriks 2013; McAlister 2005). Without discussing the illness itself, patients may not understand the need for treatment and the associated risks of their condition. Those interventions that are disease specific may prove more successful in targeting the particular concerns of the target population.

A further consideration is that the participants in these trial cohorts may exhibit a number of co-morbidities which have not been accounted for; thus, they may have received similar behaviour change interventions in the past for conditions such as diabetes, potentially increasing their knowledge and awareness of risk. Therefore, the results of these trials may not be representative of the effect a behavioural or educational intervention may have on a sample of VKA-naive AF-only patients, and we cannot draw conclusions on the use of interventions for newly referred patients who are at greatest risk of complications. The majority of AF patients are elderly and are likely to have had some prior experience making treatment decisions for other conditions, although the VKA regimen is more complex than simply taking medication.

The primary outcome of this review was time spent in therapeutic range (TTR). Whilst pooled data from the self-monitoring trials found no improvement in TTR when compared to usual care, some evidence from the educational intervention trials suggests providing face-to-face support and resources can significantly improve TTR when compared to usual care. Indeed, one decision aid trial, also providing education, found INR control deteriorated in the usual care arm over time, but improved in the intervention group (McAlister 2005). The clinical implications of improving INR control are important as the effectiveness of treatment, including warfarin, is often undermined by low levels of adherence, and maintaining the therapeutic range of 2.0 to 3.0 is imperative for stroke risk reduction (Kirchhof 2016; Morgan 2009; White 2007). More evidence is needed to identify the specific intervention components that help to improve INR control, so that these behaviour change techniques can be adopted in the future. It is important that researchers specify intervention components in detail, utilising the behaviour change taxonomy, to enable the progression of research in the field (Michie 2009; Michie 2011; Michie 2013).

Patients that self-monitor are also educated to ensure they are able to perform the tests accurately and safely. It is therefore difficult to determine whether the education or the self-monitoring is improving health outcomes. Further, patients selected for self-monitoring tend to be younger, healthier, and better educated. Thus, they may not be representative of a general AF population (Garcia-Alamino 2010). Similarly, decision aids provide patients with education regarding treatment choices; thus, it is difficult to determine whether increases in knowledge alone may have the same effect. The delivery of the intervention could also influence the outcomes. A group-based intervention provides opportunity for social comparison, which influences patient attitudes towards their treatment and their perception of social norms.

Most trials recruited patients that had been previously taking OAT. Whilst some trials included VKA-naive patients (Clarkesmith 2013; Hendriks 2013; Thomson 2007) or inpatients starting OAT (Beyth 2000; Polek 2012), only one of the trial cohorts were exclusively VKA-naive (Clarkesmith 2013). Experience of taking a VKA could increase the risk of poor internal validity as patients may had been receiving OAT treatment long term, for up to 5.5 years prior to receiving the intervention (Christensen 2007), and may be influenced by their treatment history (for example side effects). Previous experience of the treatment may also influence adherence to recommendations, and a patient's decision to start taking the treatment in the first place (Holbrook 2005; Lip 2011). Patients may develop specific beliefs about their medications that influence the decision-making process, such as the inconvenience of regular blood tests, need for reductions in or abstinence from alcohol, and dietary restrictions (Dantas 2004; Lane 2006; Lip 2007; Lip 2011). Patients may also feel a level of protection from harm by taking a treatment (Lip 2011), thus increasing their likelihood of adopting one treatment over another. One of the trials in this review recruited patients that had previously taken part in Man-Son-Hing 1999. All of these patients had previously taken either an antiplatelet drug (60% of decision aid group versus 60% of the usual care group) or OAT (37% of the decision aid group versus 38% of the usual care group). The participants within this trial are unlikely to be representative of patients that are making treatment decisions for the first time. Firstly, they are ex-trial patients and may be more likely to have had prior treatment-related education and, secondly, they have had first-hand experience of one or both treatments. One study found that more patients chose warfarin in a decision aid trial when the drug name was blinded than when it was unblinded (Holbrook 2007), suggesting that patients are influenced by prior knowledge, beliefs surrounding medications, and perhaps any adverse events they may have suffered from. In two studies included in this review (McAlister 2005; Thomson 2007), there was a difference at baseline between groups regarding the antithrombotic therapy that patients were receiving

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(those already receiving warfarin and those not) which could have affected patients' ability to make decisions about treatment, as one of the outcomes was decision conflict. Research suggests that patients are more likely to choose their current treatment over and above another; it has been suggested that this act prevents cognitive dissonance (that is the stress of choosing a preferred treatment over actual treatment choice; Fuller 2004; Holbrook 2007; Howitt 1999; Protheroe 2000).

Quality of the evidence

Two types of bias were most prevalent within the studies. Firstly, blinding of patients to the intervention received was not possible, nor was it possible to blind the intervention facilitator, inevitably raising the risk of bias. It is unclear whether the researchers may have biased patient outcomes by treating the patients in the intervention arm differently from those in the control group. Blinding the outcome assessor (data analyst or researchers) regarding to which intervention arm the patient was assigned was undertaken in six trials (Beyth 2000; Christensen 2007; Clarkesmith 2013; Gadisseur 2003; Hendriks 2013; McAlister 2005). Trial authors must be explicit when reporting their methods and procedures to ensure accurate assessment of blinding bias and enable comparison of trials.

Inclusion bias was also evident in many studies, where the trial participants may not have been representative of the eligible participants. The percentage of eligible patients randomised was as low as 15% in the exclusively AF populations (Clarkesmith 2013), and 18% in one of the mixed cohort trials (Gadisseur 2003). Perhaps the reluctance of individuals to participate may relate to the extensive training required, particularly for self-monitoring trials, or questionnaire burden. Furthermore, many patients may refuse consent due to physical limitations, the time commitment associated with multiple training sessions or multiple follow-ups, or psychological barriers to performing self-monitoring. AF patients in particular are mostly elderly (Kannel 1998), and often highly symptomatic (Lip 2011), thus trial participation may be a burden. This could explain the small AF sample sizes in the included mixed OAT indication trials, as patients with other indications may be younger and with fewer co-morbidities.

The quality of care in the control groups may vary substantially within and between countries, and the lack of a 'standard' of usual care is one of the key limitations of the studies in this field. There is no standard provision of anticoagulation monitoring, thus trials are often comparing an intervention with an unknown entity. The educational element of the intervention may be one of the key factors in improving TTR. However, trials varied in the intensity, duration, and number of education sessions, and the education facilitator; thus, we cannot draw conclusions about the influence of each of the educational components or the facilitator of these interventions on outcomes.

Five studies did not record patients' level of education (Christensen 2007; Gadisseur 2003; Polek 2012; Thomson 2007; Voller 2005), a factor which may impact on knowledge uptake and treatment control. Research suggests that patients with greater knowledge of their treatment spend more time in the therapeutic range (Tang 2003). Thus, the results of the trials that do not indicate education level may be influenced by individual differences in educational achievement between trial groups.

Whilst the educational components of the interventions did focus on important areas of risk (that is, side effects and medication recommendations), only three of the trials included education specific to the patient's indication for treatment (Clarkesmith 2013; Hendriks 2013; McAlister 2005). Studies suggest that AF patients have limited knowledge of their condition (Coehlo-Dantas 2004; Lane 2006; Lane 2015; Nadar 2003; Tang 2003), which may influence the perceptions they form about their illness and their treatment (Steed 2010). Thus, it is essential that patients form accurate concepts of their illness and make appropriate lifestyle changes.

Few studies provided AF-specific data on psychological outcomes such as anxiety, depression, and QoL. Those that did found elevated levels of anxiety and depression for AF patients in both the intervention and usual care groups (Clarkesmith 2013; Hendriks 2013). Whilst levels decreased over time, there is no evidence that this change is specifically related to the intervention. The decision aid trial that reported anxiety as an outcome also found that anxiety fell significantly in both groups from pre- to post-clinic (MD -4.57, 95% CI -6.30 to -2.84), but there was no evidence of a significant difference in anxiety between the two groups ($F(1, 95) = 0.001$; $P = 0.98$; Thomson 2007). While there is evidence to suggest that AF patients suffer from high levels of anxiety (Thrall 2004), none of the interventions in this review were designed with this in mind. Thus the trials exhibit small reductions in anxiety in the intervention groups versus usual care. As evidence suggests that AF patients often have inaccurate illness representations (Steed 2010), more trials of interventions that include targeted psychological components and outcome measures are needed.

Potential biases in the review process

Our search strategy included a comprehensive search of several electronic databases, meticulous handsearching of reference lists of included and excluded papers, recent conference proceedings, and personal communications with experts in this area. In addition, we wrote to all the authors of included studies requesting AF-specific data and further demographic and clinical details on the included cohorts. Further, the titles and abstracts of all studies identified by the search strategy were reviewed independently by two review authors and disagreements were resolved by consensus. Data extraction of the included studies was also undertaken independently by two review authors. Therefore, we believe that the potential for bias in the review process was minimal and that it is

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unlikely that we have missed important studies. It is also important to note that the authors of Clarkesmith 2013 are also authors of this review; for further details see the Declarations of interest.

AUTHORS' CONCLUSIONS

Implications for practice

Patients participating in both educational interventions and self-monitoring interventions (with education) appear to spend more time within the therapeutic INR range, but pooled analyses of the AF data did not significantly favour self-monitoring plus education over usual care. Evidence is limited, as there were few trials with small samples of AF patients. More trials are needed to examine the impact of intensive educational interventions on anticoagulation control in AF patients and the impact on TTR. Self-monitoring may not be a feasible option for many patients, particularly as it requires additional training and is costly (Fitzmaurice 2000), and new anticoagulants are now available which do not require monitoring (Lip 2011; Shantsila 2010). Further, NOAC trials - for example, where dabigatran was compared with warfarin - examined the TTR of those patients taking warfarin and compared the event rates by quartile of centre TTR (cTTR; Wallentin 2010). Despite very good cTTR (> 72.6%), both doses of dabigatran were associated with fewer adverse events than warfarin. Despite the increasing use of NOACs there are still be some patients for whom the NOACs are not suitable (for example, those with severe renal impairment), where a VKA would be the only alternative OAT treatment. However, no study to date has compared self-monitoring with a VKA to treatment with NOACs on adverse events (stroke and major bleeding) and therefore it is unclear whether there would be a benefit of self-monitoring with a VKA (in the appropriate patient) over treatment with NOACs. Given that NOACs are increasingly used to treat AF patients, there is a need for interventions to provide effective illness-specific educational tools, which incorporate relevant behaviour change techniques (Michie 2011; Michie 2013).

Implications for research

This review highlights the need for AF-specific trials of educational/behavioural interventions in larger cohorts and the development of psychological interventions for psychological morbidity in this population. Further, interventions should specifically state which behaviour change techniques they have used (and why) and their effect, in order to allow conclusions about which factors are likely to impact upon adherence. The number of VKA-naive AF patients within the trials was limited, with most patients being VKA-experienced. Trials also need to consider the use of disease-specific measuring tools, which may provide a more accurate assessment of the impact of the intervention. In addition, such trials should account for the potential confounding effects of level of education and the quality of the care in the control group.

Ongoing trials

A trial focusing on self-management is currently being undertaken (Siebenhofer 2012). This trial may provide additional evidence for later review updates. We will update this review once the results from this study are published. In addition, for the results to be generalisable to the AF population there is a need for population-based studies that collect data on adverse event rates, time in therapeutic range, and cost effectiveness, and factors that impinge on successful educational and behavioural interventions. Future studies should set out to understand the mechanisms by which interventions are successful by exploring the psychological and practical implications for AF patients commencing OAT treatment.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Beyth 2000

Methods	Randomised, controlled, parallel-groups design
Participants	**N randomised:** 132 versus 162 usual care **Diagnosis of patients:** AF n = 54 (16.6%) for the intervention group and usual care groups. Other indications include VTE, cerebrovascular disease, heart valve prosthesis, peripheral vascular disease, myocardial infarction **Demographics for total cohort:** Age: 74.9±6.9 intervention versus 74.5±6.6 usual care % female: 55% intervention versus 59% usual care % white: 69% intervention versus 65% usual care Mean number of school years 12.1±4.4 intervention versus 12.1±4.1 usual care **Demographics for AF patients:** Age: 74.6±6.8 intervention versus 75.5± 6.2 usual care % female: 40% intervention versus 66% usual care % white: 77% intervention versus 77% usual care Mean number of school years 14.5±4.9 intervention versus 12.0±3.9 usual care **Inclusion/exclusion criteria:** Patients hospitalised and receiving 10,000 units or more of intravenous heparin, were 65 years or over, for whom warfarin treatment was planned for 10 days or more. Patients were excluded if they had been treated with warfarin at any time in the previous six months, were admitted from a nursing home, were enrolled in another clinical trial, were too ill to give consent, or did not speak English
Interventions	**Type:** Guideline-based consultation, education and self-monitoring **Content:** A consultation that assessed the patients' indication for therapy and potential risks for warfarin-related bleeding (a method used by the researchers previously). This included specific recommendations about modifiable risk factors, such as use of non-steroidal anti-inflammatory drugs. The other component included patient education, coaching, and self monitoring. Patient education consisted of one to one teaching by a lay educator using a specifically formatted workbook for older adults to teach them about warfarin, indications for its use, drug and food interactions, and the signs and symptoms of bleeding. Coaching aimed to increase patients' participation in their care and improve information-seeking skills. Self-monitoring of prothrombin time (grounded in social learning theory). Patients were instructed to monitor 3 times in the first week and once weekly after that **Duration:** 30 minutes to one hour (consultation) **Facilitator:** lay educator **Setting:** hospital
Outcomes	incidence of major bleeding excessive anticoagulation rates of VTE
Country	Cleveland, Ohio, USA

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Beyth 2000 (*Continued*)

Comparison	usual care group
Length follow-up	six months
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were stratified according to their baseline risk for major bleeding by using the outpatient bleeding risk index. The index includes four independent risk factors for major bleeding: age 65 or older, history of gastrointestinal bleeding, history of stroke, and one or more of four specific comorbid conditions (myocardial infarction, hematocrit < 30%, creatinine concentration> 133µmol/L (1.5mg/dL), or diabetes mellitus). Patients with one or two risk factors were classified as intermediate risk, and those with three or more risk factors were classified as high risk; estimated frequencies of major bleeding in six months were 6% and 35% respectively. Details on how patients were assigned to treatment groups was not reported
Allocation concealment (selection bias)	Unclear risk	Of the 426 eligible patients identified, 294 (69.0%) received either usual care or the intervention. Details on how patients were assigned to treatment groups was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants cannot be blinded to which arm of the trial they receive. Neither can the personnel delivering the intervention be blinded. However, the educational intervention was delivered by a lay educator who was not involved in the treatment of the patients
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trained abstractors who were not involved with the intervention component of the study collected data from the medical chart at the start of OAT, and by blinded interview at enrolment, at one, three, and

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		six months after enrolment, and every six months thereafter. Whenever an event was reported, the clinical characteristics of the bleeding or thromboembolic episode were determined by review of the relevant medical record and abstracted, without identifying the patient, onto a standard form
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 163 patients assigned to the intervention group, 81% (n = 132) participated in the intervention; 12 patients felt more comfortable with venepuncture, three stopped warfarin during hospitalisation, and one was discharged to a nursing home that precluded the use of a portable monitor. At six months, 21 patients (13%) in the intervention group and 26 (16%) of the usual care group had died
Selective reporting (reporting bias)	Low risk	The method section describes the primary outcome as first major bleeding event during the six month intervention period. Secondary outcomes were death and recurrent VTE at six months; major bleeding after six months, and INR control during the first six months of therapy. The authors report data on all of these outcomes
Other bias	Unclear risk	All patients had to be able to self-monitor their INR and therefore the patients may not be representative of all patients requiring oral anticoagulation. However, all patients were aged 65 years or older, which is representative of an AF cohort

Christensen 2007

Methods	Open-label randomised controlled trial, cross-over (six months)
Participants	**N randomised:** 47 versus 45 (usual care/conventional management) **AF:** n = 11 versus n = 9 (usual care); other indications include mechanical heart valve, coagulopathies, VTE, synthetic vascular graft **Demographics for total cohort:** Age: 51.5±14.4 intervention versus 46.3±13.4 usual care % female: 23% intervention versus 44% usual care % white: not stated % education above primary level: not stated **Demographics for AF cohort:**

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	Age: 59±18 intervention versus 51±12 usual care % female: 0% intervention versus 7% usual care % white: 100% in both groups % high school or greater: 4% intervention versus 3% usual care **Inclusion/exclusion criteria:** Patients were eligible if they were referred for patient self-management by a general practitioner or hospital department, treated with oral anticoagulants > 8 months, 18 years or over, and willing to be randomised. Patients were excluded if they had previously used self-management or lived abroad
Interventions	**Type:** teaching lesson (not explained in detail) and patient self-management **Content:** The group used Coagucheck, which displays the INR value after the application of a drop of blood. Self-management training included the patient practicing analysis of blood specimens. The patient gradually assumed management of OAT. After 27 weeks, patients took an exam; if passed, patient went on to self-manage. After six months the conventional management group started the same training **Duration:** not stated **Facilitator:** not stated **Setting:** hospital
Outcomes	major complications (bleeding and thromboembolism requiring intervention) death and/or discontinuation of the study primary endpoint: variance of INR in trial and control samples TTR
Country	Aarhus, Denmark
Comparison	conventional management
Length follow-up	Observation period 1) 8 to 12 months before randomisation 2) primary observation period was 6 months of either patient self-management or conventional management 3) patient self-management training was 27 weeks
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to patient self-management using a computerised, prospective randomisation schedule. Randomisation in blocks with various sizes in numbers of two, four, and six was used

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Christensen 2007 (*Continued*)

Allocation concealment (selection bias)	Low risk	Of the 105 patients who were eligible to take part in the study, 100 patients were randomised (95%), therefore there is a low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the intervention, the participants receiving the intervention and the personnel delivering it cannot be blinded to which arm of the intervention they are in. It was unclear whether the personnel delivering the intervention were also involved in treating the usual care arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	External control blood samples were blinded. The results of the INR analysis were blinded for all except one secretary who would ensure the safety of the patient by contacting the managing physician if the INR value was below 1.5 or above 4.5
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the self-management arm, three patients dropped out, two during the training period, and one died. In the usual care arm of the study, one patient was withdrawn by the physician and four dropped out during the self-management training. Thus 92% of original cohort participants were included in the analysis
Selective reporting (reporting bias)	Low risk	The endpoints were the variance (mean square of standard deviation) of the INR value, the median INR value (using a blinded control sample analysed monthly by a reference laboratory) and the coumarin dose. All outcomes were reported
Other bias	High risk	All participants had to be eligible for self-management of oral anticoagulation and therefore may not be representative of all patients requiring oral anticoagulation

Clarkesmith 2013

Methods	Randomised controlled trial
Participants	**N randomised:** 46 intervention versus 51 usual care **Diagnosis of patients:** All warfarin-naive AF patients **Demographics for total cohort:**

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	Age: 72.0±8.2 intervention versus 73.7±8.1 usual care % female: 32.6% intervention versus 37.3% usual care % white: 100% intervention versus 98% usual care % education above primary level: not stated **Inclusion/exclusion criteria:** Newly diagnosed AF patients referred for warfarin therapy, with ECG-documented AF. Patients were excluded if they were aged < 18 years, had any contraindication to warfarin, had previously received warfarin, had valvular heart disease, were cognitively impaired, were unable to speak or read English, or had any disease likely to cause their death within 12 months
Interventions	**Type:** one-off, group (one to six patients), theory-driven educational intervention **Content:** The intervention involved one group session for one hour where patients were shown a DVD containing information about the need for OAT, risks and benefits, potential interactions with food, drugs and alcohol, and the importance of monitoring and control of their INR. Patients were encouraged to ask questions and complete a worksheet-based exercise following each 10 minute DVD section. They were then given educational materials such as a booklet and a self-monitoring INR and lifestyle diary to take home Usual care involved patients receiving the standard 'yellow booklet' which contains generic information for all patients taking OAT and key safety information **Duration:** one hour session **Facilitator:** health psychologist (could be delivered by trained lay educator) **Setting:** hospital outpatients clinic
Outcomes	TTR, knowledge, illness perceptions, beliefs about medication, anxiety and depression, quality of life, stroke, thromboembolic events, major and minor bleeding
Country	United Kingdom
Comparison	usual care
Length follow-up	12 months
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer generated list stratified by (a) age (< 70 and > 70 years)/sex and (b) specialist AF clinic versus 'general' cardiology clinic, in blocks of four, randomised patients on an individual basis to receive either 'usual care' or the intensive educational intervention in addition to 'usual care'. The randomisation schedule was designed by an independent trials unit

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Clarkesmith 2013 (*Continued*)

Allocation concealment (selection bias)	High risk	Of the 646 patients who were eligible for the study, 97 patients participated (15%); 234 (36.2%) eligible patients declined to participate, primarily due to the questionnaire burden. Due to the number of patients declining to participate, there is an increased risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of the intervention, the patients and staff delivering the intervention could not be blinded regarding to which arm of the trial participants were assigned. However, monitoring of the INR (for the primary outcome, TTR) was undertaken independent of the study, by the Anticoagulation Services at the hospitals (who were not aware of the patients' allocation to intervention or usual care)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The researcher analysing the data was blinded regarding to which arm of the intervention patients were randomised. A researcher not involved in the data analysis or intervention delivery matched patient ID numbers with randomisation codes and checked follow-up questionnaires for completeness
Incomplete outcome data (attrition bias) All outcomes	High risk	Ninety-seven patients were randomised to the study; one discontinued from the intervention arm due to mental health problems and one discontinued from the usual care arm due to questionnaire burden. Results were analysed based on the intention-to-treat analysis for the primary outcome (TTR). The number of patients returning questionnaires assessing the secondary outcomes was 62.9% at six months and 54.6% at twelve months
Selective reporting (reporting bias)	Low risk	All specified outcomes other than cost-effectiveness were reported
Other bias	Unclear risk	The intervention was delivered by a health psychologist and therefore the results may not be generalisable to different intervention facilitators

Gadisseur 2003

Methods	Multicentre randomised study, four arms
Participants	**N randomised:** A) weekly self-measurement n = 52; B) weekly self measurement and self-dosing n = 47; C) educated routine care n = 60; D) existing routine care (not trained) n = 161. This study used a Zelen design **Diagnosis of patients:** AF patients in group A = 6 (11.6%); group B = 9 (19.2%), group C = 10 (16.6%), and group D = 43 (26.7%). Other indications included deep vein thrombosis, pulmonary embolism, artificial heart valves, and vascular prosthesis

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	Demographics for total cohort: Age: mean in group A = 54.8 (25 to 74), B = 53.9 (24 to 75), C = 56 (21 to 73), D = 62 (32 to 75) % female: A = 23%, B = 32%, C = 40%, D = 46% % white: not stated % education above primary level: not stated **Demographics for the AF patients:** not provided **Inclusion/exclusion criteria:** At least three months of OAT experience, need for long-term OAT, and aged 18 to 75 years. Patients were excluded if they had antiphospholipid syndrome, a life threatening illness, life expectancy ≤ 1 year, diminished understanding, and physical limitations making successful participation impossible
Interventions	**Type:** self-management and self-dosing including education **Content:** They received information about the study, the blood coagulation system, OAT, and the effects of some substances (e.g. alcohol, certain medications, and foods rich in vitamin K) on OAT. They were also taught how to use the Coagucheck device, and instructed on oral self-dosing of phenprocoumon and acenocoumarol. This also contained practical information about working with the Coagucheck, information about the coagulation system, and theoretical and practical self-dosing training. They were also given written information on all the topics discussed Group A: weekly INR self-measurement, but dosing was performed by anticoagulation clinic physicians. Patients reported their INR values by telephone to the anticoagulation clinics. Dosing schedules were communicated via telephone Group B: this group self-managed their OAT, patients informed the anticoagulation clinic of their INR measurements, proposed dosing schedules, and reported any relevant information or complications. Patients were contacted via telephone to confirm whether they could adhere to their proposed dosing schedule or if they needed to adjust it Group C: patients were trained for inclusion in groups A or B but stayed with the routine care system. Measurements of INR and dosing were done by anticoagulation clinic physicians, and the interval between INR measurements depended on the stability of the INR values Group D: patients in this group were unaware of their participation in the study, representing the existing care system **Duration:** three training sessions, groups of four to five, 90 to 120 minutes **Facilitator:** delivered by physician, paramedical person **Setting:** hospital
Outcomes	Quality of OAT determined by number of INR readings in target range; occurrence of thromboembolic and haemorrhagic complications; patients ability to independently perform anticoagulant self-dosing
Country	Netherlands
Comparison	A) weekly self-measurement B) weekly self-measurement and self-dosing C) educated routine care D) existing routine care (not trained)

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Length follow-up	mean follow-up time 24.5 weeks
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The patients were selected by groups of 40 and randomised to four treatment groups (A, B, C, and D) following a 2-step partial Zelen design
Allocation concealment (selection bias)	High risk	Of the 881 eligible participants, 159 (18%) were randomised, therefore this study is at high risk of inclusion bias. 916 patients were randomly selected by a computer; 35 (3. 9%) were excluded because of intellectual or physical limitations or because of a life expectancy of < 1 year
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients who were not randomised to group D were sent a letter with written information about the study (thus not blinded). Knowledge of the composition of the different groups was restricted to a few nurses who were also responsible for anonymously transferring the dosing schedules for group A and group B patients to standard forms and faxing them to the other participating anticoagulation clinics. The patients and staff could not be blinded regarding to which arm of the trial participants were assigned. The authors do not state whether those physicians delivering the intervention also treated the usual care arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The physicians evaluating and correcting the proposed dosing schedules for group A and B were unaware of the originators of these schedules. The INR values of the patients in routine care groups C and D were entered into the routine computerised system in such a way that the dosing physicians could not distinguish between these and the general patient population

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Incomplete outcome data (attrition bias) All outcomes	High risk	Of the original 180 patients randomised to the study, 116 (64%) completed the quality of life questionnaires at baseline and follow-up; 21 patients were withdrawn or ineligible and the remainder were lost to follow-up
Selective reporting (reporting bias)	Low risk	Pre-specified endpoints were (1) quality of OAT represented by the number of INR readings within target range (TTR); (2) patients' ability to independently perform anticoagulant self-dosing, by number of dosage corrections made. All specified outcomes were reported
Other bias	High risk	All participants had to be eligible for self-management of oral anticoagulation and therefore may not be representative of all patients requiring oral anticoagulation

Hendriks 2013

Methods	Randomised controlled trial
Participants	**N randomised:** 356 intervention versus 356 usual care **Diagnosis of patients:** all AF patients **Demographics for total cohort:** Age: 66±13 intervention versus 67±12 usual care % female: 44.7% intervention versus 37.9% usual care % white: not stated % education above primary level: not stated **Inclusion/exclusion criteria:** All patients of at least 18 years of age who were referred for AF (documented on ECG) by GPs or non-cardiology specialists to their outpatient department were included. Exclusion criteria were any comorbidity which is unsatisfactorily treated, unstable heart failure defined as New York Heart Association IV or necessitating hospital admission < 3 months before inclusion, untreated hyperthyroidism, current or foreseen pacemaker, internal cardioverter defibrillator or cardio resynchronisation therapy, or cardiac surgery < 3 months before inclusion
Interventions	**Type: e**nhanced educational intervention **Content:** The intervention consisted of nurse-led outpatient care steered by decision support software based on the guidelines and supervised by a cardiologist. During the visits, the nurse specialist informed patients about the pathophysiology of AF, its symptoms and possible complications, the results of the diagnostic tests, and treatment options. The dedicated software CardioConsult AF was used to determine the individual patient profile based on symptoms, type of AF, and stroke risk, and it proposed the most appropriate management. Follow-up visits were scheduled at 3, 6, and 12 months, and every 6 months thereafter. Patients could contact the nurse in person or by telephone between planned visited as needed. Patients in the control group received usual care by

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	a cardiologist in the outpatient clinic during visits **Duration:** 30 minutes per visit **Facilitator:** nurse specialist **Setting:** Maastricht University medical centre
Outcomes	**Primary endpoint:** composite endpoint of cardiovascular hospitalisation or cardiovascular death **Secondary endpoints:** guideline adherence, patient knowledge on AF, quality of life, patient satisfaction, cost-effectiveness
Country	The Netherlands
Comparison	usual care (outpatient visits with cardiologist)
Length follow-up	at least 12 months
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to nurse-led care or usual care by a computer generated one to one randomisation
Allocation concealment (selection bias)	Low risk	Out of 760 eligible patients, 712 patients participated (94%). Therefore there is a low risk of inclusion bias. The groups were well matched without significant differences in baseline characteristics
Blinding of participants and personnel (performance bias) All outcomes	High risk	The nurse, patients, and the supervising cardiologist were not blinded due to the nature of the intervention. The authors do not state whether those physicians involved in delivering the intervention also treated the usual care arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	There was an independent panel of specialists to assess the primary endpoint. This committee was blinded to assignment and interim study outcomes. They reviewed each case independently and held a meeting at the end. If the decision was non-unanimous, the endpoint was established by the study chair
Incomplete outcome data (attrition bias) All outcomes	High risk	The final sample included all of the original patients that were randomised to the study. None of the patients were lost to follow-up. Patients (n = 178) who did not complete the SF-36 at both time-points were excluded. There is a suggestion that more usual care arm patients did not complete the SF-36 questionnaires

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Hendriks 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported with the exception of patient satisfaction
Other bias	Unclear risk	This was a nurse-led comprehensive intervention and therefore the results may not be applicable outside this setting

Man-Son-Hing 1999

Methods	Randomized controlled trial 20 possible SPAF trial centres invited, 14 participated
Participants	**N randomised:** n = 139 intervention (10 lost to follow-up) versus n = 148 control (14 lost to follow-up) **Diagnosis of patients:** all AF patients **Demographics of cohort:** Age: intervention mean = 65 versus control mean = 65 % female: intervention 24% versus control 24% % white: not stated % education above primary level: intervention 90% high school education or greater versus control 91% high school education or greater **Inclusion/exclusion criteria:** All participants were in the SPAF III aspirin cohort study and were eligible unless they had high risk criteria or had a major haemorrhage during the study
Interventions	**Type:** decision aid **Content:** 29 page booklet, a personal worksheet (complete pre-intervention), and a 20-minute audiotape that guided the patient through the booklet and worksheet. The intervention included a description of the consequences of minor/major stroke and major haemorrhage, the blood monitoring required for warfarin and the 2-year probability of stroke and major haemorrhage for patients taking aspirin/warfarin using pictograms **Duration:** not stated **Facilitator:** physician/audio tape **Setting:** hospital
Outcomes	One to four days after meeting with their physicians patients completed questionnaires: Patient choices (strength of their decisional input, five-point Likert scale, unvalidated) Knowledge (23 questions about AF, stroke and treatment, unvalidated) Expectations (four questions regarding patient expectations of stroke/haemorrhage, unvalidated) Decisional conflict (decisional conflict scale; O'Connor 1995) Satisfaction (six questions, five-point Likert scale, unvalidated) Six-month adherence to their treatment decisions (self-report brief questionnaire, administered via telephone, unvalidated)
Country	US

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Comparison	Control group, usual care, i.e. no change was made to the usual manner in which each centre communicated the results of the SPAF III study or the way in which the decision regarding type of antithrombotic was made
Length follow-up	six-month follow-up
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated scheme, administered from a central location to block sequence from previewing. Stratified by centre and the presence of a history of hypertension
Allocation concealment (selection bias)	High risk	Of the 657 patients who were eligible for the trial, 287 participated (43%), giving a substantial risk of inclusion bias; 24 participants were lost to follow-up
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors do not state whether the researcher or personnel were blinded regarding to which arm the participants were randomised. However, we can assume that participants and physicians were not blinded to treatment allocation due to the nature of the intervention. The authors do not state whether those physicians delivering the intervention also treated the usual care arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The authors do not state whether the personnel scoring and analysing the questionnaires were blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	From 139 patients participating, 87 (63%) worksheets were completed. However, all of the 139 patients randomised to the decision aid were included in the study analysis of decision conflict
Selective reporting (reporting bias)	Low risk	Outcome measures were patients' ability to make choices regarding antithrombotic therapy, six-month adherence to decision, knowledge, decision conflict and satisfaction. There was no protocol paper for this

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		study. Only one of the pre-specified outcome variables in the method section was not reported (patient satisfaction)
Other bias	High risk	This was a sub-set of the SPAF III trial and all patients were receiving aspirin. The SPAF III study excluded those who had 'high-risk criteria' (without explanation of this) and those who had major haemorrhage, both of which are likely to affect opinion about oral anticoagulation and the ability to make decisions about treatment. Those who participated had a greater proportion with better education (high school or greater) compared to those who declined participation and this could have influenced the ability to make a decision. There was the possibility of contamination between the intervention and comparator arms as physicians could have provided similar information which was contained in the educational booklet during routine clinic visits to patients in the usual care group

McAlister 2005

Methods	Prospective, multicentre, two-arm, cluster randomised trial
Participants	**N randomised:** intervention n = 219 versus control n = 215 Fifty GP practices were randomised to the decision aid group and 52 were randomised to usual care **Diagnosis of patients:** All NVAF (also broken down by type of AF; see paper) **Demographics of cohort:** Age: intervention 73±9 versus control 71±10 % female: intervention 43% versus control 34% % white: not stated % completed high school: intervention n = 84 (38%) versus control n = 72 (33%) **Inclusion/exclusion criteria:** Community-dwelling patients over the age of 18 were included in this study if they had a diagnosis of NVAF (intermittent or chronic) confirmed by ECG, or prescription for digoxin. They were excluded if they 1) had valvular AF; 2) were taking warfarin for another condition; 3) were scheduled for cardioversion; 3) had a contraindication for warfarin or aspirin; 4) had cognitive impairment; 5) had a life expectancy less than 12 months; 6) could not understand/converse in English
Interventions	**Type:** general education session plus patient decision aid and physician's manual **Content:** 30-page decision aid booklet, personal worksheet, 50-minute audiotape to guide participants through the booklet and worksheet, and a seven-page physician's manual summarising the evidence discussed in the patient booklet with a focus on the

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	2001 ACCP risk stratification schema and recommendations for antithrombotic therapy. Four versions of the decision aid were available depending on patients' baseline stroke risk. All four versions provide the same background information about AF; the potential consequences of stroke and major haemorrhage; relative efficacy/bleeding risks with warfarin and aspirin therapy. Key points are further elaborated upon in the audio-tape. The one-page worksheet is to be completed by the patient after reviewing the booklet to clarify their personal values regarding desired outcomes, the therapy they are inclined to take, their preferred role in the decision process, and any questions they have for their physician **Duration:** not stated **Facilitator:** physician **Setting:** GP practices
Outcomes	Use of appropriate antithrombotic therapy at three months, as defined by the 2001 ACCP recommendations. Secondary outcomes include (1) appropriate antithrombotic therapy at 6 months and 12 months, (2) patient's readiness to make a choice at baseline (previously validated questionnaire), (3) patient knowledge after the intervention (multiple-choice responses used in a previous trial), (4) decisional conflict (decision conflict scale; O'Connor 1995), (5) acceptability of decision aid (9 questions with variable responses on a five-point Likert scale), (6) satisfaction (five-point Likert scale), (7) adherence with therapy (validated Morisky scale with modified five-point Likert scale response)
Country	Canada
Comparison	usual care
Length follow-up	one-year follow-up
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation to intervention or usual care was carried out according to a computer-generated sequence using clustered block randomisation (block size of four) with allocation concealment
Allocation concealment (selection bias)	High risk	Of the 904 patients who were eligible for the study, 446 were randomised (49%). Due to the number of patients declining screening, there is an increased risk of inclusion bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors do not state whether the researchers or personnel were blinded regarding to which arm the participants were ran-

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		domised. However, we can assume that participants and physicians were not blinded to treatment allocation due to the nature of the intervention. Physicians who delivered the intervention did not treat the usual care arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessment was carried out by an independent statistician who was blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 446 eligible participants who were randomised, 434 (97%) were included in the three-month follow-up evaluation
Selective reporting (reporting bias)	Low risk	The primary endpoint was use of appropriate antithrombotic therapy; other endpoints include TTR, patient's readiness to make choices, knowledge, decision conflict, acceptability of decision aid, satisfaction, and adherence. Adherence and satisfaction scales data are not explained in detail. However, authors report the majority of data from the protocol paper including key primary and secondary outcomes
Other bias	High risk	There was an imbalance at baseline in antithrombotic therapy between the intervention and usual care groups which could have influenced the patients' ability to make decisions regarding antithrombotic therapy thereby affecting the outcomes. In addition, a greater proportion of patients were unwilling to consider changing treatment at baseline in the decision aid group compared to usual care (41% versus 36%) and more patients in the decision aid group felt that their physician should make the decision regarding antithrombotic therapy than those in the usual care (52% versus 40%); both of which could have affected patients' decisional conflict. The study was underpowered as the protocol paper suggested that 814 participants were required (N = 434 included)

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Polek 2012

Methods	Nested randomised controlled trial
Participants	**N randomised:** intervention = 25 versus usual care = 28 **Diagnosis of patients:** mixed indication cohort **Demographics of the cohort:** Age: mean 63.71 (SD 16.04) % female: not stated % white: not stated % education above primary level: not stated **Demographics of the AF patients:** N = 14 Treatment group n = 5; usual care n = 9 Age: mean intervention = 73.6 (SD 11.1) versus mean usual care = 76 (SD 13.4) % female: intervention = 4/5 (80%) versus usual care = 3/9 (33%) % white: intervention = 3/5 (60%) versus usual care = 5/9 (55%) % educated above primary school level: not available **Inclusion criteria:** patients discharged to home on OAT, alert and orientated, able to speak and understand English, and accessible via telephone **Exclusion criteria:** patients discharged to a nursing home or rehabilitation facility, history of psychotic disorder or cognitive impairment
Interventions	**Type:** enhanced educational intervention **Content:** face-to-face warfarin education, printed materials, instruction, medical alert bracelet. The intervention was based on Banduras social cognitive model and aimed to improve self-efficacy. Four post-discharge phone calls assessing knowledge post-intervention and correcting incorrect answers **Duration:** not stated **Facilitator:** pharmacist **Setting:** hospital
Outcomes	warfarin knowledge self-efficacy
Country	USA
Comparison	usual care
Length follow-up	12 weeks
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were randomly assigned to the intervention or usual care group after receiving patient education from the pharmacist. Authors do not describe the sequence generation

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Polek 2012 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Of 66 patients who were screened and offered participation in the study, there were 53 included in the original randomised sample (80% of those screened), with a low risk of inclusion bias. Only 42/53 (79%) received the intervention or usual care; 42/66 of eligible patients were therefore included (64%)
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors do not state whether the researchers or personnel were blinded regarding to which arm the participants were randomised. However, we can assume that participants and physicians were not blinded to treatment allocation due to the nature of the intervention. The authors do not state whether the personnel delivering the intervention also treated the usual care arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors do not state whether the person scoring the questionnaires was blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	The final sample included 42 (79%) of the original 53 patients that were randomised to the study. Attrition was 36% and therefore designated as high risk of bias
Selective reporting (reporting bias)	Low risk	The authors describe two outcomes in their method section: (1) warfarin knowledge and (2) self-efficacy. The authors report on both outcomes in their results section. There was no published protocol paper, thus we cannot determine whether those outcomes reported reflect those that were included in the study
Other bias	High risk	Very small sample size (N = 42 in total)

Thomson 2007

Methods	Three/two-armed open, randomised controlled efficacy trial
Participants	**N randomised:** 69 decision aid versus 67 guidelines **Diagnosis of patients**: all AF patients **Demographics of cohort:** Age: 73.1±6.7 decision aid versus 73.7±6.2 guidelines % female: 43.4 decision aid versus 44.6 guidelines % white: not stated % education above primary level: not stated **Inclusion/exclusion criteria:** Patients were recruited if they were already taking warfarin

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	or if they were considering taking warfarin for the first time. Patients were eligible if they were aged 60 or over and had either chronic NVAF or PAF. Patients were excluded if they had acute onset AF requiring cardioversion, previous stroke or TIA, contraindications for warfarin, or cognitive impairment, or were taking warfarin for other indications, non-English speaking, or at risk of cerebral bleed
Interventions	**Type:** decision aid **Content:** included individual risk and benefit presentation and a section to support shared decision making Two different decision aids: 1. Used explicit value elicitation employing the standard gamble method and Markov decision analysis "explicit tool" 2. Included only risk/benefit presentation "implicit tool" (computerised decision aid). The doctor was trained to use the computerised decision aid Early in the trial, the observation study (running alongside the trial) found the first decision aid to be difficult, so this arm was discontinued (gamble method) and the paper describes the results of the second arm versus evidence-based paper guidelines. The intervention arm included benefits and harms of warfarin treatment, advantages and disadvantages, and personalised risk assessment (using the Framingham equation). The presentation used graphical and numerical forms of presentation **Duration:** mean 31 minutes long (range 16 to 41) **Facilitator:** computerised tool **Setting:** research clinic
Outcomes	decision conflict knowledge state trait anxiety inventory Degner's decision making preference scale
Country	Newcastle, UK
Comparison	guideline-based consultation
Length follow-up	three months
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised to either computerised decision aid (intervention) or evidence-based paper guidelines (control), using electronically-generated random permuted blocks via a web-based randomisation service provided by the Centre for Health Services Research

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Allocation concealment (selection bias)	High risk	Of 483 patients who were eligible for the study, 145 patients were eventually randomised (30%). Thus there is a substantial risk of inclusion bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors do not state whether the researchers or personnel were blinded regarding to which arm the participants were randomised. However, we can assume that participants and physicians were not blinded to treatment allocation due to the nature of the intervention. The authors do not state whether those physicians delivering the intervention also treated the usual care arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The authors do not state whether the person scoring the questionnaires was blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of the 69 patients allocated to the decision aid tool, 16 (23%) did not receive the intervention. Of the 67 patients allocated to the guidelines group, 11 (16%) did not receive the intervention. In total, 19% of patients randomised did not receive the intervention. More patients randomised to the decision aid tool did not receive the intervention although the overall attrition rate was < 20%. Reasons included withdrawal of consent, death, illness, surgery, alcoholism, and inability to use the tool
Selective reporting (reporting bias)	Unclear risk	The primary outcome was decision conflict. Secondary outcomes were state and trait anxiety, knowledge, and decision making preference. Decision conflict outcomes were reported, but there was no tabulated report of the scale breakdown. All of the outcomes were reported, but mean scores and numbers of patients per group were not
Other bias	Unclear risk	There was a difference at baseline between the groups in the number of patients not already receiving warfarin which may have influenced patients' ability/willingness to make treatment decisions which may have affected the primary outcome (decisional conflict)

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Voller 2005

Methods	Prospective multicentre randomised controlled trial
Participants	**N randomised:** 101 self-management versus 101 family doctor group **Diagnosis of patients**: all NVAF patients **Demographics of cohort:** Age: 64.6±9.6 self-management versus 64.1±8.9 family doctor % female: 28.6 self-management versus 38.6 family doctor % white: not stated % education above primary level: not stated **Inclusion/exclusion criteria:** All patients for whom long-term anticoagulation was indicated because of permanent non-valvular AF were included into the investigation. Exclusion criteria were lack of suitability for INR self-management, participation in another study, alcohol or other addiction, a mechanical heart valve replacement or anticoagulant treatment already administered for another indication, and diseases such as AIDS or carcinomas. Patients with visual impairment were also excluded
Interventions	**Content:** educational session following the standards of the Working Group for the Study of Patient Self-Management of Oral Anticoagulation, based on the intervention session developed by Sawicki and colleagues. The programme consisted of three consecutive weekly teaching sessions for groups of three to six patients. Topics included anticoagulation in general, INR self-monitoring, preventing bleeding, effects of diet and other medication, reducing or increasing dose, problems that may be encountered with operations, illness, exercise, pregnancy, etc **Duration:** 60 to 90 minutes (based on Sawicki's description) **Facilitator:** not stated **Setting:** not stated
Outcomes	**Primary endpoint:** number of thromboembolic or hemorrhagic complications requiring treatment **Secondary endpoints:** the degree of handicap after stroke, the degree of severity of haemorrhage, the proportion as well as cumulative time of the INR values in the individual target range, INR variance, time course of complications, and the cost efficiency of self-measurement compared to conventional procedures
Country	Germany
Comparison	family doctor group
Length follow-up	Overall observation period (retrospective): self-management 37.34±5.93 years family doctor 40.25±6.07 years
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

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Random sequence generation (selection bias)	Low risk	Randomisation list developed before beginning of the study with SAS software PROC PLAN procedure
Allocation concealment (selection bias)	Unclear risk	Authors do not report how many participants were eligible for the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors do not state whether the researcher or personnel were blinded regarding to which arm the participants were randomised. However, we can assume that participants and physicians were not blinded to treatment allocation due to the nature of the intervention. The authors do not state whether those physicians delivering the intervention also treated the usual care arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The authors do not state whether the person scoring the questionnaires was blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All of the 202 patients who were randomised to the study were included in the final analysis
Selective reporting (reporting bias)	High risk	The study was discontinued because the number of cases was too small, and the group comparison was confined to the evaluation of the number of INR values measured and the total period for which the patients remained outside, above, and below the target range
Other bias	High risk	All patients had to be eligible for self-management of oral anticoagulation and therefore may not be representative of all AF patients requiring oral anticoagulation. The mean age was 64 years which is fairly young for an AF population. In addition, there were only three primary outcome events (two haemorrhages in the self-management group and one thromboembolic event in the family doctor group)

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Vormfelde 2014

Methods	Cluster randomised controlled trial of 22 GP practices
Participants	**N randomised:** intervention = 185 patients versus comparator = 134 patients **Diagnosis of patients:** AF, thrombosis, pulmonary embolism, heart valve replacement, unknown **Demographics for total cohort:** Age: 73±10 intervention versus 72±10 usual care % female: 56% intervention versus 58% usual care % white: not stated % education above primary level: not stated **Demographics of the AF patients:** N = 14 Treatment group n = 141 versus usual care n = 81 Age: intervention mean 74.5 (SD 8.0) versus usual care mean 72.9 (SD 9.4) Female: intervention = 72 (45.6%) versus usual care = 38 (46.9%) ≥ 10 years education: intervention 32 (20.3%) versus usual care 28 (34.6%) **Inclusion/exclusion criteria:** All patients taking OAT (with a range of indications) with ability to consent to participation and adequate German language skills were included. Exclusion criteria included residence in a nursing home and patients in cross coverage
Interventions	**Type:** parallell randomised controlled trial **Content:** Practice nurses delivered the educational intervention session consisting of a 20-minute video presentation, an eight-page brochure, and a corresponding questionnaire. The information was on 13 topics pertaining to oral anticoagulation with phenprocoumon according to the internationally recognised model and recommendations. Usual care included patients who were only given a brochure **Duration:** one hour **Facilitator:** practice nurse **Setting:** general practice
Outcomes	Primary outcome: number of correctly answered questions from the 13-item OAT questionnaire Secondary outcomes: time spent in therapeutic range, subjective feelings of safety and complications related to OAT
Country	Germany
Comparison	patients who were only given the brochure
Length follow-up	six months
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The first 22 GPs that agreed to participate were included. The Institute for Medical Statistics randomised these 22 practices

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		into two equal-sized trial groups (intervention versus control) by random permutation
Allocation concealment (selection bias)	High risk	Of the 85 general medical practices contacted, 22 general medical practices agreed to participate (26%). There is risk of bias from participation of more highly motivated and better educated individuals than average, who knew they were being tested
Blinding of participants and personnel (performance bias) All outcomes	High risk	The authors do not state whether the researchers or personnel were blinded regarding to which arm the participants were randomised. However, we can assume that participants and practice nurses were not blinded to treatment allocation due to the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The authors do not state whether their data analysis was blinded regarding to which group the patients were randomised
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 979 anticoagulated patients who were identified in the 22 practices, 319 completed the trial (33%). During follow-up, for the intervention arm (n = 194), nine (5%) did not complete the trial as eight moved away and one died. For the control arm (n = 151), 17 (11%) patients did not complete the trial as six moved away, three died, and eight chose to drop out. INR analysis was possible in 157/194 (81%) patients in the intervention group and 91/151 (60%) in the control arm; overall attrition was greater than 20% and more patients in the control group did not have INR data at follow-up available for the analyses
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	High risk	Improvement in knowledge was dependent on the practice where the patient education was delivered which was probably due to differences in the discussion with the nurse after the video presentation

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

Study	Reason for exclusion
Al-Meshal 2013	No breakdown of patient group
Armstrong 2011	Not an RCT
Bajorek 2005	Not an RCT, no control group
Baker 1991	Wrong patient group, no AF
Barcellona 2006	No unpublished AF data provided on request
Batty 2001	Does not measure any of the required outcomes
Bereznicki 2013	No separate control group, patients acted as their own historical control
Blaise 2009	Not an RCT, retrospective study
Bloomfield 2011	Meta-analysis, not an RCT
Bump 1977	No AF patients
Burns 2009	Not an RCT, review paper
Castelino 2010	Not an RCT
Chan 2006	No unpublished AF data provided on request
Christensen 2011	Limited education, specific to self-testing
Claes 2005	No AF patients
Claes 2006	No AF patients
Corbella 2009	Not an RCT
Cordasco 2009	No AF patients
Cromheecke 2000	No AF patients
Cromheecke 2001	No AF patients
Davis 2005	Not an RCT, survey
Dolor 2010	No education other than instruction to self-test

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(*Continued*)

Duran-Parrondo 2011	Trial is not randomised
Field 2010	Training is for staff not patients
Fitzmaurice 1996	Not a patient intervention
Fitzmaurice 2000	Did not include an educational or behavioural intervention
Fitzmaurice 2005	No AF patients
Fraenkel 2011	Not compared to usual care, not an RCT
Gardiner 2006	No unpublished AF data provided on request
Gouin-Thibault 2010	Intervention for staff not patients
Grunau 2011	Patients were educated on self-monitoring only
Hasan 2011	Not an RCT
Heidbuchel 2015	Not an RCT, review article
Holbrook 2007	No AF patients
Jackson 2004	Does not measure any of the required outcomes
Jank 2009	No unpublished AF data provided on request
Khan 2004	Randomisation procedure did not meet inclusion criteria
Krause 2010	Systematic review not an RCT
Lakshmi 2013	No unpublished AF data provided on request
Landefeld 1992	No AF patients
Leger 2004	Not an RCT, wrong patient group
Machtinger 2007	No unpublished AF data provided on request
Matchar 2005	No education or behaviour change within the intervention
Matchar 2010	Self-monitoring only, no educational or behavioural intervention
Mazor 2007	No AF patients
McCahon 2011	No breakdown of patient group

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(*Continued*)

Megden 1999	Not an RCT
Menendez-Jandula 2005	No unpublished AF data provided on request
Moore 2013	No breakdown of patient group
Morin 2015	Not an RCT, research model
Moss 2014	No unpublished AF data provided on request
Nedaz 2002	Not an RCT, this paper is a commentary
Nilsson 2011	Abstract only, no mention of AF patients
O'Sullivan 2016	Does not include any of the primary or secondary outcomes
Peng 2014	Does not include any of the primary or secondary outcomes
Pernod 2008	No AF patients
Polzien 2007	Not an RCT, commentary
PRISM Study group 2003	Does not include any of the primary or secondary outcomes
Qvist 2016	Not an RCT, no comparison group
Reverdin 2011	Not an RCT
Ryan 2009	No unpublished AF data provided on request
Saokaew 2010	Systematic review and meta-analysis, not an RCT
Satger 2009	Not an RCT, review article
Sawicki 1999	No unpublished AF data provided on request
Sawicki 2003	Not an RCT, no comparison group
Siebenhofer 2007	No unpublished AF data provided on request
Stafford 2011	Not a randomised trial
Stone 1989	No unpublished AF data provided on request
Sunderji 2005	Education only relates to self-monitoring
Suriano 2014	No breakdown of patient group

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(*Continued*)

Taylor 1997	Not an RCT
Trivalle 2010	Education of staff not patients
Tuiskula 2011	Not an RCT
Turc-Dessertine 2005	Not an RCT, survey. No intervention or control group
Vadher 1996	No breakdown of patient group
Vadher 1997	No breakdown of patient group
Verret 2012	No breakdown of patient group
Waterman 2001	No AF patients, no comparison group
Waterman 2001 b	No patient intervention
Watzke 2000	No unpublished AF data provided on request
Winans 2010	Not an RCT
Witt 2005	Not an RCT, retrospective, observational cohort study
Woodend 2005	Not an RCT (commentary)
Wurster 2006	Not an RCT
Yildirim 2015	No unpublished AF data provided on request

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

Siebenhofer 2012

Trial name or title	Primary Care Management for Optimized Antithrombotic Treatment [PICANT]
Methods	Cluster randomised controlled trial
Participants	Patients with an indication for oral anticoagulation
Interventions	Patient information leaflet and a video developed by Vormfelde 2014, treatment monitoring via the Coagulation Monitoring List, and encouragement to participate in a self-management course where they will learn how to carry out self-testing and self-dosing

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Siebenhofer 2012 (*Continued*)

Outcomes	**Primary outcome**: combined endpoint of all thromboembolic events requiring hospitalisation and all major bleeding complications **Secondary outcomes**: mortality, hospitalisation, stroke, major bleeding and thromboembolic complications, severe treatment interactions, number of adverse events, quality of anticoagulation, health-related quality of life, and costs
Starting date	July 2012
Contact information	siebenhofer@allgemeinmedizin.uni-frankfurt.de
Notes	

ACCP: American College of Clinical Pharmacy
AF: atrial fibrillation
ECG: Electrocardiography
GP: general practitioner
INR: international normalised ratio
NVAF: nonvalvular atrial fibrillation
OAT: oral anticoagulation therapy
PAF: paroxysmal atrial fibrillation
SPAF Stroke Prevention in Atrial Fibrillation Study
TIA: transient ischemic attack
TTR: time in therapeutic range
VTE: venous thromboembolism

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DATA AND ANALYSES

Comparison 1. Self-monitoring plus education versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time in therapeutic INR range	2	69	Mean Difference (IV, Fixed, 95% CI)	6.31 [-5.63, 18.25]

Comparison 2. Education versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HADS anxiety	2	587	Mean Difference (IV, Fixed, 95% CI)	-0.62 [-1.21, -0.04]
2 HADS depression	2	587	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-1.34, -0.14]

Comparison 3. Decision-aid versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Decision conflict	2	721	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.17, -0.02]

WHAT'S NEW

Last assessed as up-to-date: 8 February 2016.

Date	Event	Description
1 November 2016	New search has been performed	This is an update of the original search and review published in 2013. This update has added an additional 10 articles based on 3 studies (Clarkesmith 2013; Hendriks 2013; Vormfelde 2014). The additional studies were all educational interventions. Data from two of these trials (Hendriks 2013; Clarkesmith 2013) on anxiety and depression were pooled (Analysis 2.1; Analysis 2.2). Data from the additional trials were also included (but not pooled) for time in therapeutic range, education, quality of life, beliefs about medication, and cost effective-

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		ness. A summary of findings table has been added to the update (Summary of findings for the main comparison) .
1 November 2016	New citation required and conclusions have changed	Three additional trials reported in this update compared with 2013 review. Additional data contributed to novel synthesis of analysis of effects on anxiety and depression

CONTRIBUTIONS OF AUTHORS

Data collection, paper searches, screening and appraisal, and data extraction were conducted by Miss Khaing and Drs Clarkesmith and Lane. Dr Clarkesmith wrote the initial draft of the Introduction and Methods of the review paper, which was edited by Dr Lane. Drs Clarkesmith and Lane performed the data analysis together and drafted the Results and Discussion sections. Both Dr Clarkesmith and Dr Lane revised and commented on subsequent drafts. Professor Pattison contributed to the interpretation of the analyses and provided critical revision of drafts of the review.

DECLARATIONS OF INTEREST

Dr Clarkesmith completed a PhD studentship that was funded by an Investigator-Initiated Educational Grant from Bayer Healthcare and Aston University when the original review was conducted, but currently works as a post-doctoral researcher with no conflicts of interest. Miss Khaing reports no conflicts of interest. Dr Lane was the principal grant holder for the 'TRial of an Educational intervention on patients' knowledge of Atrial fibrillation and anticoagulant therapy, INR control, and outcome of Treatment with warfarin' (TREAT). Dr Clarkesmith was the primary investigator for TREAT. Dr Lane and Professor Pattison were the educational supervisors of Dr Clarkesmith for the TREAT study. This review is not funded by Bayer Healthcare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Contributions of the authors

The contributions of authors has changed from the original protocol (see contributions of authors section).

2. Decision conflict as a secondary outcome

Decision conflict was included as a secondary outcome in the final analysis. Whilst not specified as an outcome of interest in the original protocol, it was highlighted as a common secondary outcome measure in three of the studies included in the final review. For this reason, the authors decided to include these data within the results.

INDEX TERMS

Medical Subject Headings (MeSH)

*International Normalized Ratio [standards]; *Patient Education as Topic; Administration, Oral; Anticoagulants [*administration & dosage; adverse effects]; Atrial Fibrillation [blood; *complications]; Chronic Disease; Decision Support Techniques; Drug Monitoring [*methods; standards]; Medication Adherence; Randomized Controlled Trials as Topic; Self Care [methods]; Stroke [blood; etiology; *prevention & control]

MeSH check words

Aged; Humans; Middle Aged

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