Self-monitoring and self-management of oral anticoagulation (Review)

Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D, Heneghan CJ

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TABLE OF CONTENTS

[Intervention Review]

Self-monitoring and self-management of oral anticoagulation

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ABSTRACT

Background

The introduction of portable monitors (point-of-care devices) for the management of patients on oral anticoagulation allows self-testing by the patient at home. Patients who self-test can either adjust their medication according to a pre-determined dose-INR schedule (self-management) or they can call a clinic to be told the appropriate dose adjustment (self-monitoring). Several trials of self-monitoring of oral anticoagulant therapy suggest this may be equal to or better than standard monitoring.

Objectives

To evaluate the effects of self-monitoring or self-management of oral anticoagulant therapy compared to standard monitoring.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 4), MEDLINE, EMBASE and CINAHL (to November 2007). We checked bibliographies and contacted manufacturers and authors of relevant studies. No language restrictions were applied.

Selection criteria

Outcomes analysed were thromboembolic events, mortality, major haemorrhage, minor haemorrhage, tests in therapeutic range, frequency of testing, and feasibility of self-monitoring and self-management.

Data collection and analysis

The review authors independently extracted data. We used a fixed-effect model with the Mantzel-Haenzel method to calculate the pooled risk ratio (RR) and Peto's method to verify the results for uncommon outcomes. We examined heterogeneity amongst studies with the Chi^2 and I^2 statistics.

Main results

We identified 18 randomized trials (4723 participants). Pooled estimates 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). This reduction in mortality remained significant after the removal of low-quality studies (RR 0.65, 95% CI 0.46 to 0.90). Trials of self-management alone showed significant reductions in thromboembolic events (RR 0.47, 95% CI 0.31 to 0.70) and all-cause mortality (RR 0.55, 95% CI 0.36 to 0.84); self-monitoring did not (thrombotic events RR 0.57, 95% CI 0.32 to 1.00; mortality RR 0.84, 95% CI 0.50 to 1.41). Self-monitoring significantly reduced major haemorrhages (RR 0.56, 95% CI 0.35 to 0.91) whilst self-management did not (RR 1.12, 95% CI 0.78 to 1.61). Twelve trials reported improvements in the percentage of mean INR measurements in the therapeutic range. No heterogeneity was identified in any of these comparisons.

Authors' conclusions

Compared to standard monitoring, patients who self-monitor or self-manage can improve the quality of their oral anticoagulation therapy. The number of thromboembolic events and mortality were decreased without increases in harms. However, self-monitoring or self-management were not feasible for up to half of the patients requiring anticoagulant therapy. Reasons included patient refusal, exclusion by their general practitioner, and inability to complete training.

PLAIN LANGUAGE SUMMARY

Self-monitoring and self-management of oral anticoagulation therapy

Near patient or point-of-care testing devices have made it possible for people on long-term oral anticoagulation to monitor their blood clotting time measured as the international normalized ration (INR) in the home setting. Patients who self-test can either adjust their medication dose according to a pre-determined dose-INR schedule (self-management) or they can call a clinic to be told the appropriate dose adjustment (self-monitoring). Several published studies suggest these methods of monitoring anticoagulation therapy may be equal to or better than standard monitoring by a physician.

In total, we found 18 randomized trials that compared self-monitoring and self-management with standard monitoring. The combined results of these trials showed a halving of thromboembolic events and all-cause mortality with self-monitoring and self-management and no reduction in the number of major bleeds. Self-management had similar reductions in thromboembolic events and mortality to the overall benefit, with no effect on major bleeds. Self-monitoring halved the number of major haemorrhages that occurred but did not significantly reduce the rates of thrombotic events or all-cause mortality.

In conclusion, self-monitoring or self-management can improve the quality of oral anticoagulant therapy, leading to fewer thromboembolic events and lower mortality, without a reduction in the number of major bleeds. Self-monitoring and self-management are not feasible for all patients, which requires the identification and education of suitable patients.

BACKGROUND

Oral anticoagulation therapy with vitamin K antagonists has been shown to reduce thromboembolic events (Connolly 1991; Corporative 1990; SPAF 1996; EAFT 1993; Ezekowitz 1992; Go 2003) in multiple clinical contexts. These include atrial fibrillation, treatment of deep-vein thrombosis, prosthetic heart valves, and acute myocardial infarction. Optimal anticoagulation with warfarin or other vitamin k antagonists like acenocumarole or phenprocoumon could potentially prevent more than half of the strokes related to atrial fibrillation and heart valve replacements with a relatively low risk of major bleeding complications (Buckingham 2002); however, much of this potential is still not obtained because of under and suboptimal use (Stafford 1998).

The number of patients receiving oral anticoagulant drugs has been constantly increasing during the last decade. Reasons include improvements in clinical outcomes, increasing common disease indications for their use (Manotti 2001), and improvements in anticoagulant safety (Ansell 2001). In 1994, 250,000 patients in the United Kingdom were receiving anticoagulant therapy

(Baglin 1994); 10 years later this number had increased to around 950,000 patients (Fitzmaurice 2005). Vitamin k antagonist (warfarin, acenocumarole, or phenprocoumon) treatment usually requires regular monitoring of prothrombin time (PT) with dose-adjustment by a specialized hospital service, primary care physician, registered nurse, nurse practitioner, or pharmacist (Hirsh 1998).

Numerous obstacles to the use of warfarin exist; including practical, patient, physician, and healthcare system-related barriers. Due to the complex pharmacokinetics of warfarin, continuous monitoring and dose adjustments are required. Different values and preferences amongst physicians and patients about the relative importance of bleeding and thromboembolic events, non-adherence to drug treatment, non-adherence to clinical guidelines, drug interactions, and increased costs of monitoring and therapy all have significant roles to play in the management of anticoagulation therapy (Heneghan 2008).

Vitamin k antagonists belong to the drug class known as coumarins. They produce their anticoagulant effect by interfering with the metabolism of vitamin k. There are various different types of coumarins but warfarin is the most prescribed drug. Warfarin has a high bioavailability (Breckenridge 1978) and is rapidly absorbed from the gastrointestinal tract so that maximal blood concentrations are reached 90 minutes after oral administration. Warfarin has a half-life of 36 to 42 hours; in the blood it is bound to plasma proteins (mainly albumin). It accumulates in the liver where the two isomers are metabolically transformed by different pathways (Ansell 2004). Another vitamin K antagonist is acenocumarole, which has a similar action to warfarin but differs in some pharmacological properties (for example it has a shorter half life and a lower risk of haemorrhage). The maximum activity of both drugs is reached within one or two days of treatment and the anticoagulant effect is maintained for approximately two days after stopping treatment with acenocumarole and between two and five days with warfarin. Phenprocoumon is another vitamin k antagonist that has traditionally been the oral anticoagulant of choice in Europe. It has similar actions to other vitamin k antagonists but has a half-life of 144 hours. As a result of their pharmacokinetic properties, these agents interact with many other drugs and their blood levels are affected by vitamin k intake in the diet, changes in metabolism, and concomitant illnesses, which makes the levels difficult to control (Greenblatt 2005).

The pharmacodynamics of warfarin are subject to genetic and environmental variability (Hirsh 2001) such that there is considerable variation in the action of these drugs both between different individuals (inter-individually) and within the same individual (intra-individually). A 'therapeutic target range' has been established to deal with this variability and is expressed as the international normalized ratio (INR). This INR was established as a standard way of reporting the prothrombin time (PT). Furthermore, using the INR formula (INR = patient PT/mean normal PT) the ratio between patient PT and normal PT is calculated to the power of the ISI (International Sensitivity Index), which is the conversion factor for the used thromboplastin against the WHO standard.

The 'therapeutic range' for anticoagulants is narrow. INR values over 4.5 increase the risk of major bleeding and an INR less than 2 increases the risk of thromboembolism (Cannegieter 1995; Hylek 1996; Kearon 2003). The inter and intra-individual variability and the narrow target range requires frequent testing and appropriate adjustment of the drug dose. In addition, time within the therapeutic INR target range is highly dependent on the frequency of testing (Horstkotte 1998). Different values and preferences amongst patients and physicians have also been described with the former willing to accept a much higher risk of bleeding for an associated reduction in risk of stroke (Devereaux 2001).

An economic model analysed the cost of suboptimal oral anticoagulation and showed the following. If 50% of those not receiving warfarin prophylaxis had optimal anticoagulation, 19,380 emboli would be prevented and 1.1 billion US dollars could be saved. If 50% of those currently receiving warfarin as part of routine medical care had optimal anticoagulation, 9852 emboli would be prevented and 1.3 billion US dollars could be saved (Caro 2004).

Current models of oral anticoagulation management within the UK include the traditional hospital outpatient model and various forms of community-based models, all requiring patient attendance at a clinic (Fitzmaurice 2002). In other countries, such as Canada, a primary care physician monitors the INR and adjusts the warfarin dose (Sunderji 2004).

The introduction of portable monitors (point-of-care devices) allows the patient to self-test at home with a drop of whole blood. Portable monitors for monitoring long-term oral anticoagulation were introduced in the 1990s. Portable monitors have proved to be reliable with regard to analytical accuracy, although INR measurements tend to be lower with the portable coagulometers compared to laboratory analysers (Christensen 2009; Poller 2006).

Generally patients receive a structured educational programme given by the nurses or physicians responsible for their care. In addition, they receive training in self-testing, instructions to prevent bleeding and thromboembolic complications, and are made aware of the effects of diet and medications. Patients who self-test can either adjust their therapy according to a pre-determined dose-INR schedule (self-management) or they can call a clinic to be told the appropriate dose adjustment (self-monitoring).

In some countries, such as Germany, self-monitoring and self-management with portable monitors are established therapeutic methods. There are several available point-of-care devices and the most well known is the CoaguChek® monitor. Other available monitors are the ProTime® Microcoagulation System, INRatio® Monitor, Hemochron Junior Signature, and the TAS near-patient test system. Potential advantages of self-monitoring and self-man-

agement include improved convenience for patients, better treatment adherence, more frequent monitoring, and fewer thromboembolic and haemorrhagic complications (Taborski 1999). Near-patient testing devices have made self-testing of anticoagulation therapy with vitamin k antagonists possible. Guidelines generally do not endorse self-monitoring or self-management (Fitzmaurice 2001) despite several authors of trials suggesting this approach may be equal to or better than standard monitoring (Anderson 1993; Cromheecke 2000; Sawicki 1999). A recent study suggested that self-monitoring and self-management are cost-effective strategies for those receiving long-term oral anticoagulation (Regier 2006).

To establish the strength of the available evidence, we conducted a systematic review of the impact of patient self-monitoring or self-management on treatment with oral anticoagulation therapy.

Terminology

- Point-of-care testing (POC): diagnostic testing performed in a clinic, home, or other site of patient care (rather than in standard reference laboratory)
- Point-of-care device: portable monitor used by a healthcare provider (physician, nurse, or other) or patient to determine a clinical measure
- Self-monitoring: the trained patient uses point-of-care testing to perform the INR test and inform his or her healthcare provider of the result. The physician or another healthcare provider adjusts the anticoagulant dose using the results obtained by the patient
- Self-management: trained patient uses point-of-care testing to perform the INR test, interpret the result, and adjust the dosage of anticoagulant accordingly (adapted from Brown 2007)

OBJECTIVES

To evaluate the effects on thrombotic events, major haemorrhages, and all-cause mortality of self-monitoring or self-management of oral anticoagulation compared to standard monitoring.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) assessing the therapeutic effectiveness and safety of self-monitoring or self-management of oral anticoagulation therapy.

Types of participants

All patients, adults and children, on long-term anticoagulant therapy (treatment duration longer than two months) irrespective of the indication for treatment (for example valve replacement, venous thromboembolism, atrial fibrillation).

Types of interventions

Self-monitoring or self-management of oral anticoagulation as compared to:

1. control of and dosage by personal physician;
2. anticoagulation managed services (hospital anticoagulation service);
3. anticoagulation clinics (management conducted by registered nurses, nurse practitioners, or pharmacists using dosage-adjustment protocols).

Types of outcome measures

Primary outcome measures

- Thromboembolic events
- Mortality from all causes
- Major haemorrhage (e.g. haemorrhage requiring hospital admission or transfusion)
- Time in range, and proportion of measurements within the therapeutic range for each particular condition

Secondary outcomes

- Minor haemorrhage (e.g. bleeding after minor trauma, nose bleed)
- Frequency of testing
- Feasibility of testing: patient factors (e.g. physical limitations), and non-patient factors (e.g. inability to attend training)
- Quality of life and general satisfaction with treatment

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 4), MEDLINE on PubMed (1966 to November 2007), EMBASE (1980

to November 2007), and CINAHL (1982 to November 2007). We limited our searches to randomized controlled trials by using a maximally sensitive strategy adapted to each database (Dickersin 1994; Lefebvre 1996). The full search strategies are available in Appendix 1.

Searching other resources

We searched for ongoing trials (for example on the UK National Research Register, Trials Central, Current Controlled Trials) and handsearched reference lists of all retrieved papers. We contacted Roche® Diagnostics (one manufacturer of PT and INR monitors) in order to identify further published and unpublished studies. There were no language restrictions.

Data collection and analysis

Data extraction

Two review authors (JM, PA) screened studies for inclusion and retrieved all potentially relevant studies. Three review authors (JM, PA, CH) independently extracted data on study population, intervention, pre-specified outcomes, methodology, and quality from eligible trials. The review authors were not blinded to any aspect of the studies (for example journal type, authors' names, institution). We resolved disagreements by consensus. If needed, we sought additional information from authors. We used Cohen's kappa to assess agreement between the two review authors on the selection of articles for inclusion.

We extracted information on disease characteristics and training provided to the different groups. In the self-management group we extracted information on the actions patients subsequently undertook. We extracted the characteristics of the population studied, including the number of and reasons for participants not entering the trial (for example refusal or exclusion). Additionally, we sought information on the reasons for discontinuation by participants allocated to the intervention.

In the case of cross-over studies, the outcomes of interest are potentially confounded by the cross-over and we only used data from the first part of the trial (before cross-over).

Quality assessment

Three review authors (JM, PA, CH) independently extracted methodological information for the assessment of internal validity. They used the following five components: method of randomization, concealment of allocation, intention to treat, number of and reasons for patient losses to follow up, and blinding. We did a sensitivity analyses for study quality by including only those studies with clear methods of randomization and concealment of allocation (high quality studies). We also used GRADE to assess the quality of the included studies.

Quantitative data synthesis

For the analysis we used Review Manager (RevMan) Version 5.0. For the statistical analysis we calculated relative risks (RRs) and 95% confidence intervals (CIs) as summary statistics. We used a fixed-effect model with the Mantzel-Haenzel method to calculate the pooled odds ratio; and Peto's method to verify the results in uncommon outcomes. We examined heterogeneity amongst studies with the Chi^2 and I^2 statistics (Higgins 2003). Where significant heterogeneity existed we used the random-effects model (DerSimonian 1986).

We examined publication bias by constructing a funnel plot of precision (SE of the log RR) against RR for the endpoints of major haemorrhage and thromboembolic episodes. We performed a sensitivity analysis by excluding low quality studies and pre-specified subgroup analyses according to clinical indication (mechanical valve replacement or atrial fibrillation), and self-monitoring or self-management therapy. We performed a post-hoc subgroup analysis according to who provided the control group care (specialist anticoagulation clinic, family physician). Meta-regression in STATA tested any subgroup interaction on the outcomes. The ratio of the average test frequency per individual patient/year between intervention and control groups was calculated and linear regression was used to assess the association with study duration. Pooling of the mean percentage of tests in the therapeutic range was not possible; results were summarized using means and ranges. We tested subgroup interactions using meta-regression (Intercooled STATA 9.1 for Windows).

To provide further insight into the adequacy of the total sample size across all trials we calculated a posteriori the optimal information needed for our meta-analysis (Pogue 1997). To determine this optimal information size we assumed a 2% risk of thromboembolism (median control event rate from trials in the review) and a 50% RR reduction with a power of 95% and a two-sided alpha = 0.01.

RESULTS

Description of studies

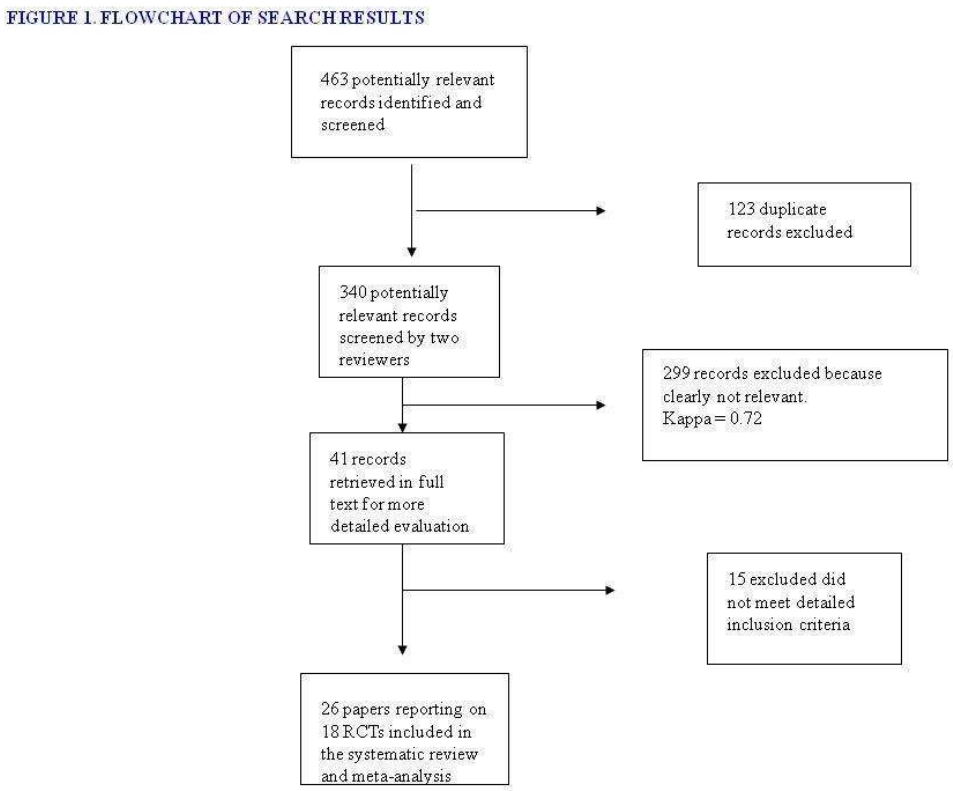
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

We identified 463 citations of which 123 duplicate records were excluded, leaving 340 potentially relevant studies. We independently reviewed 41 retrieved articles for inclusion and data extraction. One additional unpublished trial was included after the initial screen (Kaatz Unpublished).

Two review authors achieved good agreement in the initial selection of trial titles for inclusion (kappa 0.72, 95% CI 0.59 to 0.86) and on the inclusion of full-text articles (kappa 0.81, 95% CI 0.62 to 1.01).

A total of 18 trials that compared self-monitoring or self-management of oral anticoagulation to standard monitoring met the eligibility criteria (Figure 1). These trials were published between 1989 and 2007 and were largely undertaken in Europe (five in UK; four in Germany; two in Netherlands; one in each of Spain, Denmark, and Austria); five were undertaken in United States and Canada. In total, 4723 participants on long-term anticoagulation were included in our analysis. All studies but one (Cromheecke 2000) used a cross-over design. We located one unpublished study and were given access to the complete data by the authors (Kaatz Unpublished).

Figure 1.



One trial (Gadisseur 2003 Self mge; Gadisseur 2003 Self monit) presented results on four groups. One group used self-management therapy (Gadisseur 2003 Self mge), one used self-monitoring therapy (Gadisseur 2003 Self monit). The two other arms with no self-monitoring were combined (trained and untrained patients) to provide an overall control group and were then subdivided for the independent comparisons.

Three trials included only participants on life-long anticoagulation therapy following mechanical valve insertion (Horstkotte 1998; Körtke 2001; Sidhu 2001); two trials included participants on long-term anticoagulation for atrial fibrillation (Khan

2004; Voller 2005); 13 trials included participants on long-term anticoagulation for any indication (Beyth 2000; Christensen 2006; Cromheecke 2000; Fitzmaurice 2002; Fitzmaurice 2005; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Gardiner 2005; Kaatz Unpublished; Menendez-Jandula 2005; Sawicki 1999; Siebenhofer 2007; Sunderji 2004; White 1989). In 11 trials the intervention group used self-management (Christensen 2006; Cromheecke 2000; Fitzmaurice 2002; Fitzmaurice 2005; Körtke 2001; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Siebenhofer 2007; Sunderji 2004; Voller 2005) and six trials used self-monitoring (Beyth 2000; Gardiner 2005; Horstkotte 1998; Kaatz Unpublished; Khan 2004; White 1989). One further trial (Gadisseur 2003 Self mge; Gadisseur 2003 Self monit) reported information on both self-management and self-monitoring groups. Eight trials used primary care for the control group (Beyth 2000; Fitzmaurice 2002; Horstkotte 1998; Körtke 2001; Sawicki 1999; Sidhu 2001; Sunderji 2004; Voller 2005) and eight studies used specialist anticoagulation clinics (Cromheecke 2000; Fitzmaurice 2005; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Gardiner 2005; Kaatz Unpublished; Khan 2004; Menendez-Jandula 2005; White 1989). In the two remaining trials patients in the control group could use either primary care or specialist clinics (Christensen 2006; Siebenhofer 2007). Duration of studies varied from two months (White 1989) to more than 24 months (Körtke 2001); the mean duration was 12 months.

Analysis of publication bias using funnel plots of major haemorrhage and thromboembolic events showed no evidence of asymmetry (Figure 2, Figure 3).

Figure 2. Funnel plot of comparison: 1 Major haemorrhage, outcome: 1.1 Events by Self-adjustment.

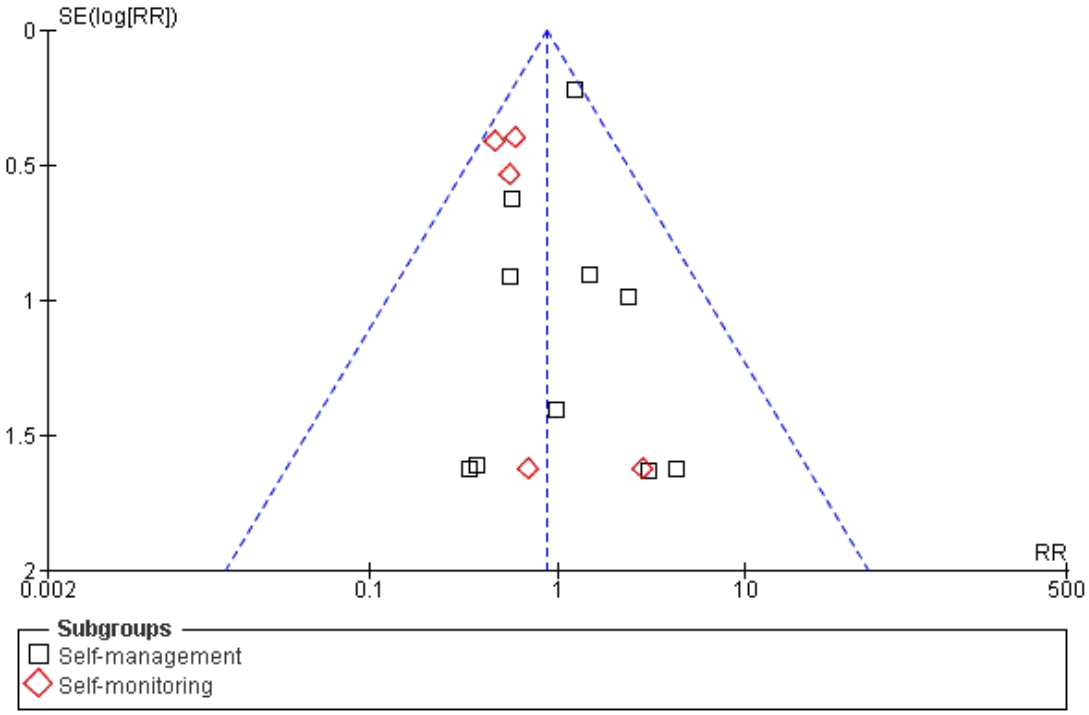
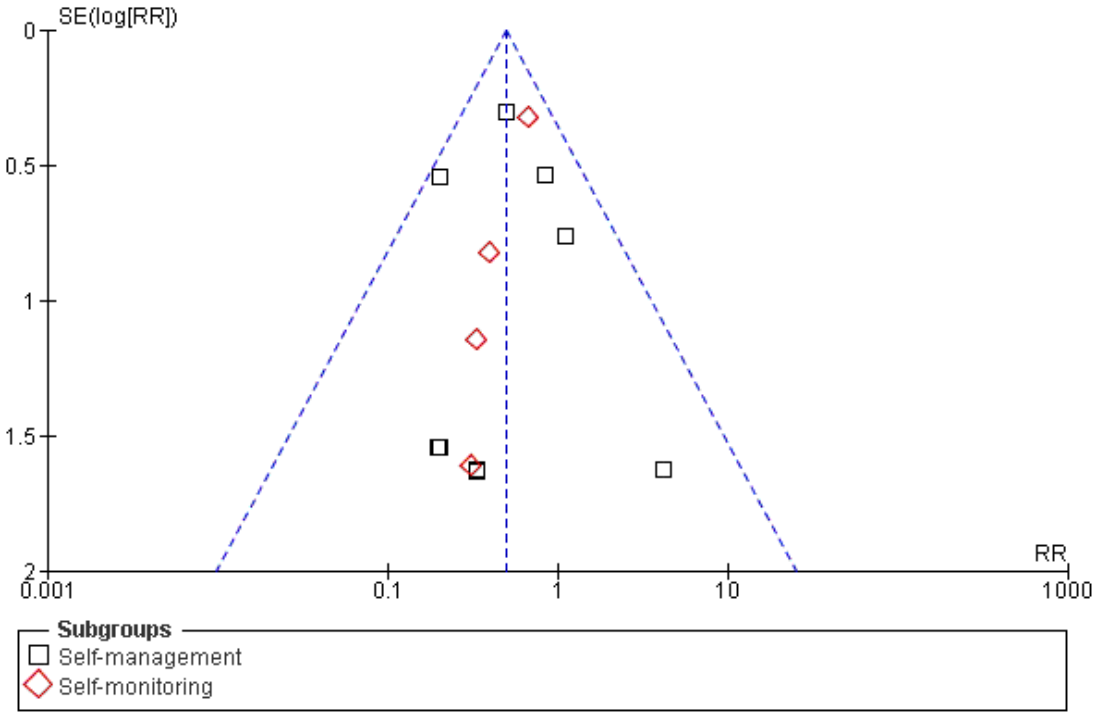


Figure 3. Funnel plot of comparison: 2 Thromboembolic events, outcome: 2.1 Events by Self-adjustment



Risk of bias in included studies

The reported quality was generally moderate. We contacted nine authors of the 18 included trials for additional details of randomisation process, concealment of allocation, and blinding. The additional information provided generally raised our ratings of the quality of the trial, indicating that authors had met methodological criteria. We also obtained valuable validity information from the ACP Journal Club structured reviews on two occasions. ACP reviews contact study authors when needed and are a valuable source of additional information for validity issues.

After the addition of extra information supplied by authors, four trials were judged to be of poor quality (Gardiner 2005; Khan 2004; Sidhu 2001; White 1989) and were removed in the sensitivity analysis. These four trials did not perform intention-to-treat analyses and allocation concealment was unclear. According to GRADE (Figure 4) the available evidence was judged to be moderate due to flaws in study design; most commonly there was an absence of information about the allocation concealment procedure or blinding and the number of events was less than 300 for the primary outcomes (Characteristics of included studies).

Figure 4. GRADE Table

Risk of Bias (GRADE)

Self-monitoring and Self management of oral anticoagulation

Patient or population: patients with oral anticoagulation
Settings:
Intervention: Self-monitoring

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Self-monitoring	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Major hemorrhage	Medium risk population		RR 0.87 (0.66 to 1.16)	4720 (19)	⊕⊕⊕O moderate[1,2]	
	12 per 1000	10 per 1000 (8 to 14)				
Thromboembolic events	Medium risk population		RR 0.5 (0.36 to 0.69)	4723 (19)	⊕⊕⊕O moderate[1,2]	
	20 per 1000	10 per 1000 (7 to 14)				
Minor hemorrhage	Medium risk population		RR 0.64 (0.54 to 0.77)	2773 (14)	⊕⊕⊕O moderate[1]	
	42 per 1000	27 per 1000 (23 to 32)				
Death	Medium risk population		RR 0.43 (0.31 to 0.59)	4080 (16)	⊕⊕⊕O moderate[1,2]	
	2 per 1000	1 per 1000 (1 to 1)				

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

CI: Confidence interval; RR: Risk ratio;

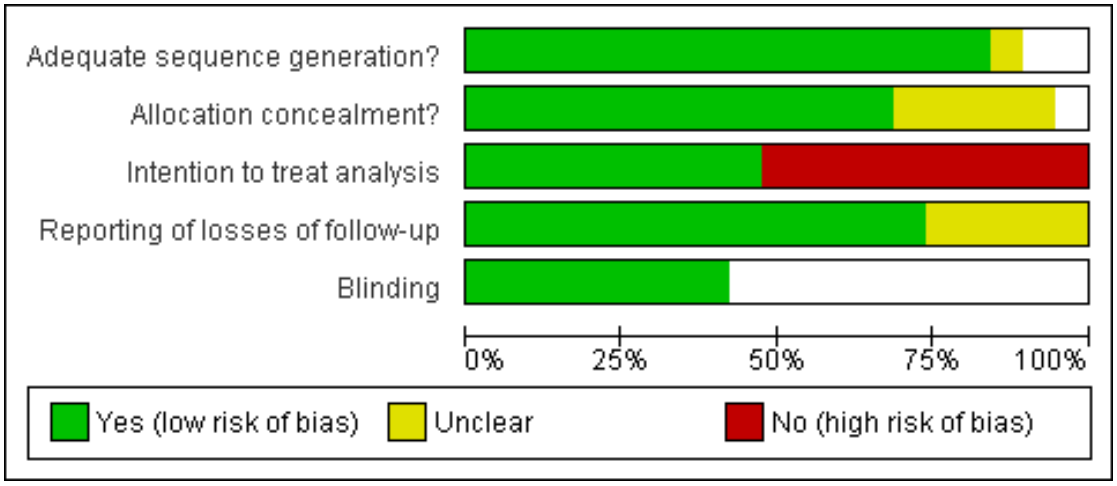
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further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

[1] Flaws in study design, most commomly an absence of information about the allocation concealment procedure or blinding.
[2] Few number of events (<300)

Randomization and allocation concealment

Fifteen studies reported adequate information about the randomization process (Christensen 2006; Cromheecke 2000; Fitzmaurice 2002; Fitzmaurice 2005; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Kaatz Unpublished; Khan 2004; Körtke 2001; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Siebenhofer 2007; Sunderji 2004; Voller 2005; White 1989). However, the method of allocation concealment was generally not reported in the published papers. After contacting authors 12 of the 18 trials had an appropriate method of concealment (Beyth 2000; Christensen 2006; Cromheecke 2000; Fitzmaurice 2002; Fitzmaurice 2005; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Kaatz Unpublished; Körtke 2001; Menendez-Jandula 2005; Sunderji 2004; Siebenhofer 2007; Voller 2005,). Four studies used both concealment of allocation and intention to treat (Christensen 2006; Fitzmaurice 2005; Menendez-Jandula 2005; Siebenhofer 2007) (see Figure 5).

Figure 5. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Blinding

Patient blinding was not possible due to the nature of the intervention. Five studies included information about blinding. Two trials blinded data collectors (Beyth 2000; Sawicki 1999), one blinded healthcare providers (Gadisseur 2003 Self mge; Gadisseur 2003 Self monit), and four trials blinded outcome assessors (Cromheecke 2000; Fitzmaurice 2005; Menendez-Jandula 2005; Siebenhofer 2007) (see Figure 5).

Follow up

Of those assigned to the intervention, 25% (range 0% to 57%) stopped self-monitoring or self-management by the end of the trial. Eight trials used an intention-to-treat analysis (Beyth 2000; Christensen 2006; Fitzmaurice 2005; Kaatz Unpublished; Menendez-Jandula 2005; Sawicki 1999; Siebenhofer 2007; Sunderji 2004). All included studies described appropriate patient follow up (see Figure 5).

Financial support

Five studies (Beyth 2000; Cromheecke 2000; Horstkotte 1998; Kaatz Unpublished; Körtke 2001) did not describe the financial support. Five studies were supported by grants from professional associations or national agencies (Christensen 2006; Fitzmaurice 2005; Khan 2004; Sunderji 2004; White 1989). Eight studies (Fitzmaurice 2002; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Gardiner 2005; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Siebenhofer 2007; Voller 2005) were part funded by an unrestricted research grant from industry (Roche Diagnostics, Boehringer) or received the coagulometer and strips for utilization during the study.

Effects of interventions

Primary endpoints

Thromboembolic events

Eighteen trials reported thromboembolic outcomes (4723 participants, 146 events); 13 trials provided the information to calculate the overall effect size (Beyth 2000; Cromheecke 2000; Fitzmaurice 2005; Horstkotte 1998; Kaatz Unpublished; Körtke 2001; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Siebenhofer 2007; Sunderji 2004; Voller 2005; White 1989). Compared to standard therapy, self-monitoring and self-management halved thromboembolic events (RR 0.50, 95% CI 0.36 to 0.69; P < 0.0001) (Figure 6). The findings were not affected by the removal of the four studies deemed to be of low quality (RR 0.49, 95% CI 0.35 to 0.68; P < 0.0001) (Figure 7). In those groups that self-managed (Cromheecke 2000; Fitzmaurice 2005; Körtke 2001; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Siebenhofer 2007; Sunderji 2004; Voller 2005) the effect was larger (RR 0.47, 95% CI 0.31 to 0.70; P = 0.0003) than in the groups that self-monitored (RR 0.57, 95% CI 0.32 to 1.00; P = 0.05) (Beyth 2000; Horstkotte 1998; Kaatz Unpublished; White 1989). However, the subgroup interaction was non-significant (P = 0.65). Compared to standard therapy, self-monitoring and self-management in patients with mechanical valves (Horstkotte

1998; Körtke 2001; Sidhu 2001) resulted in a significant effect on thromboembolic events (RR 0.53, 95% CI 0.30 to 0.91; P = 0.02) (Figure 8). The post-hoc subgroup analysis for specialised care (RR 0.42, 95% CI 0.22 to 0.84) and family physician care (RR 0.55, 95% CI 0.37 to 0.83) showed both to be significant (subgroup interaction P = 0.32).

Figure 6. Forest plot of comparison: 2 Thromboembolic events, outcome: 2.1 Events by Self-adjustment 1.

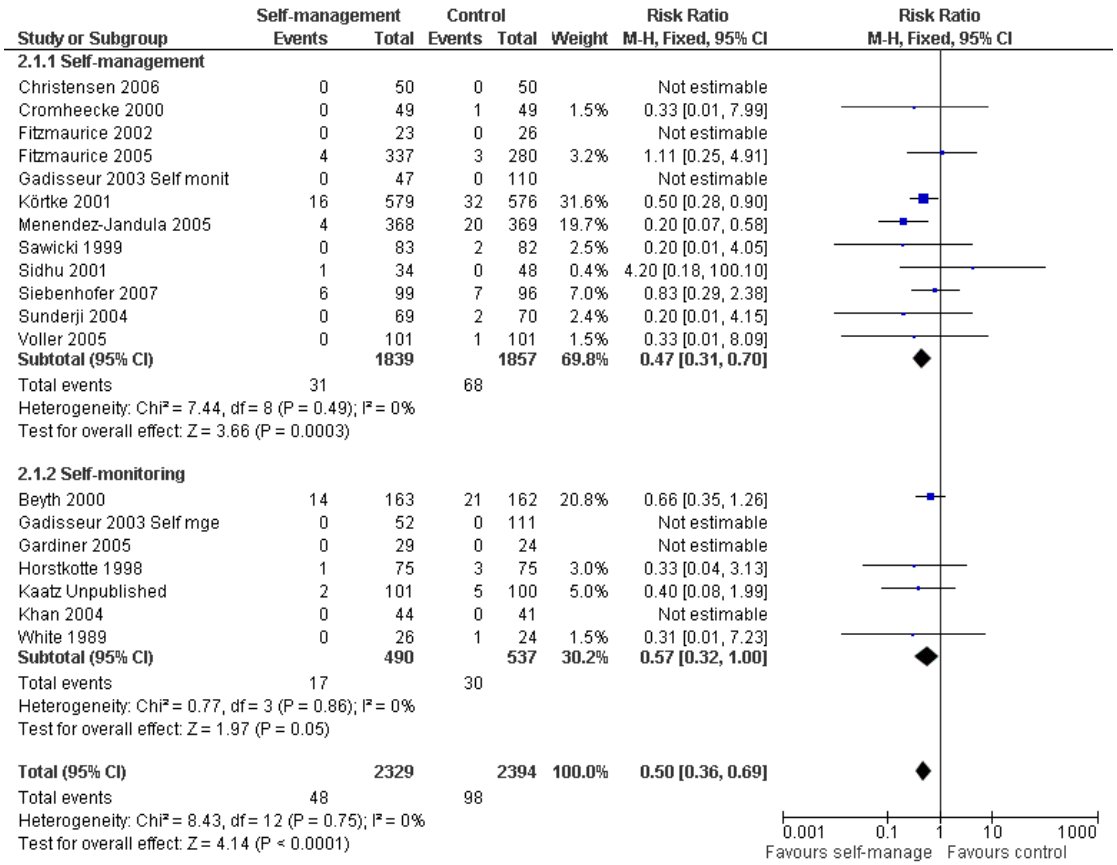


Figure 7. Forest plot of comparison: 2 Thromboembolic events, outcome: 2.3 Events by Self-adjustment (sensitivity).

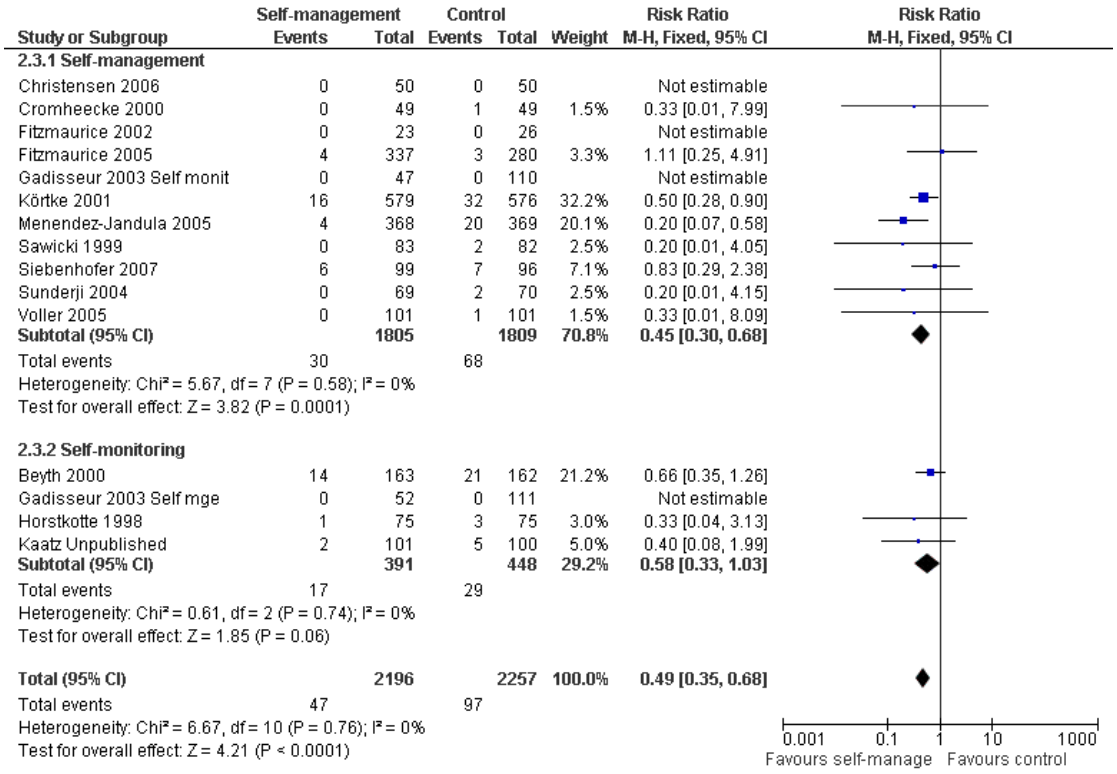
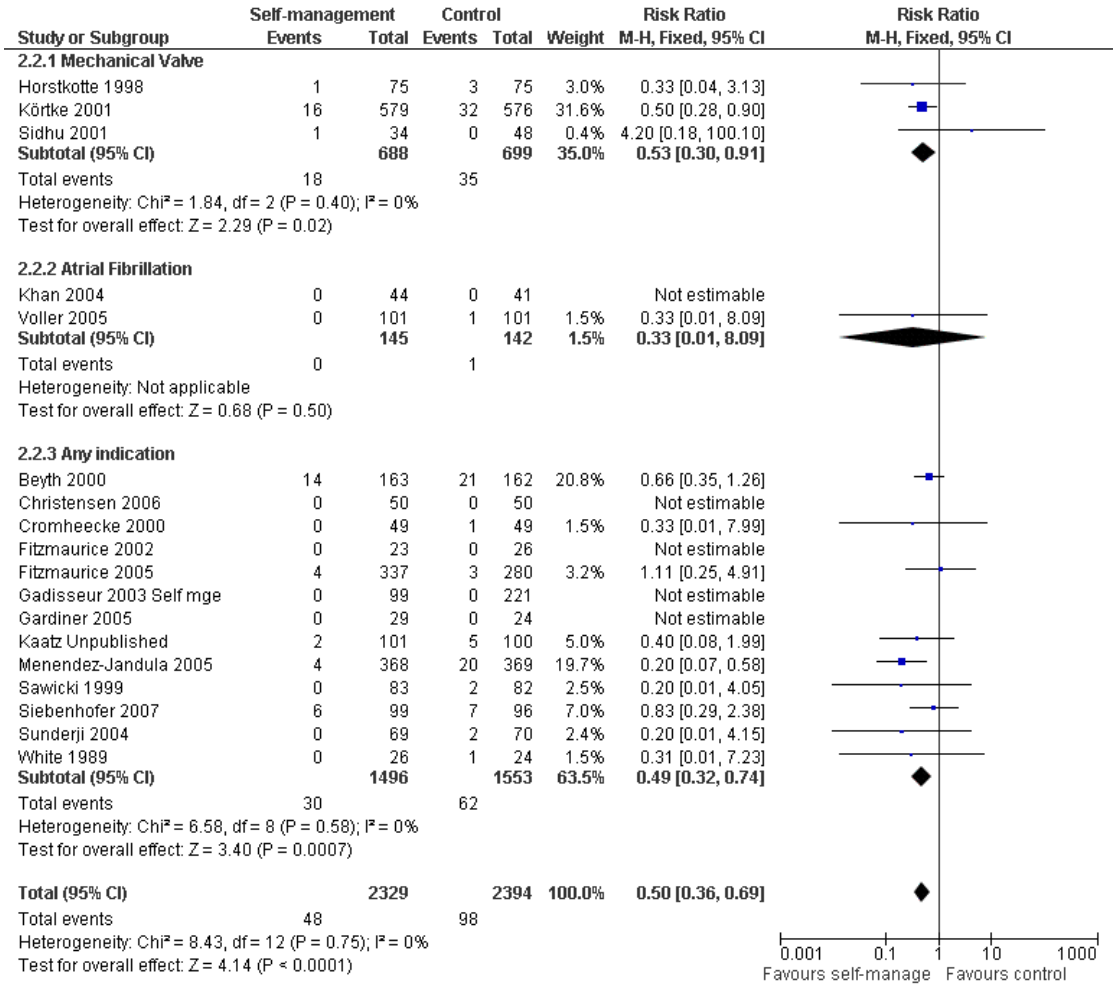


Figure 8. Forest plot of comparison: 2 Thromboembolic events, outcome: 2.2 Events by Clinical Condition.



Mortality

Sixteen trials reported information on mortality (4305 participants, 137 events); nine trials provided the information to calculate the overall effect size (Beyth 2000; Fitzmaurice 2002; Fitzmaurice 2005; Gardiner 2005; Körtke 2001; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Siebenhofer 2007). Despite only one trial showing a significant reduction in mortality the pooled estimate indicated that self-monitoring and self-management were associated with an overall reduction in mortality from all causes when compared to standard therapy (RR 0.64, 95% CI 0.46 to 0.89; P = 0.007) (Figure 9). The findings were not affected by removal of the four studies deemed to be of low quality (RR 0.65, 95% CI 0.46 to 0.90; P = 0.01) (Figure 10). In three studies of patients with mechanical valves (Horstkotte 1998; Körtke 2001; Sidhu 2001) self-monitoring and self-management showed a significant reduction in mortality (RR 0.49, 95% CI 0.28 to 0.85; P = 0.01).

Figure 9. Forest plot of comparison: 3 Mortality, outcome: 3.1 Events by Self-adjustment.

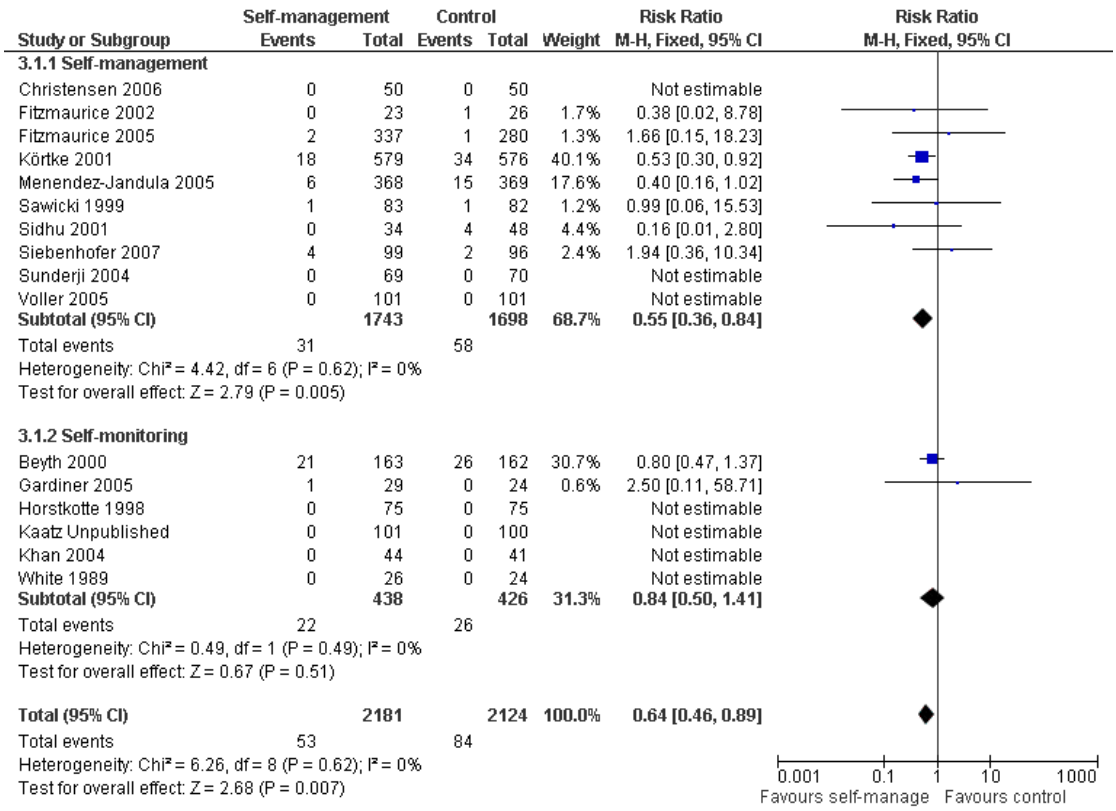
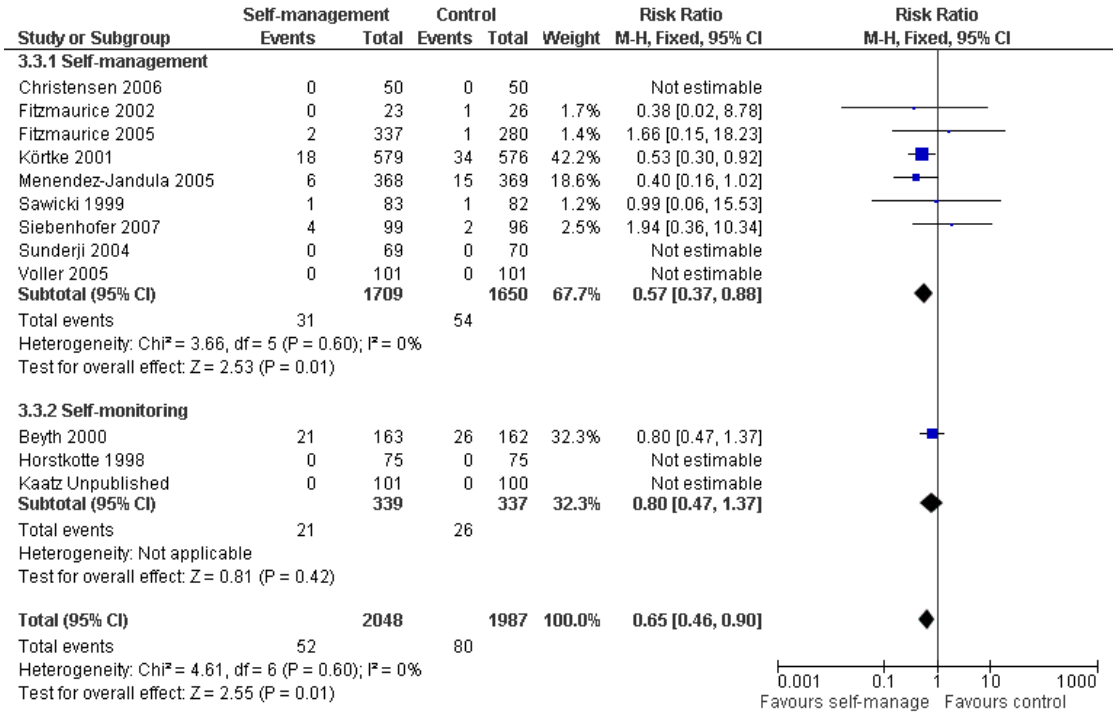
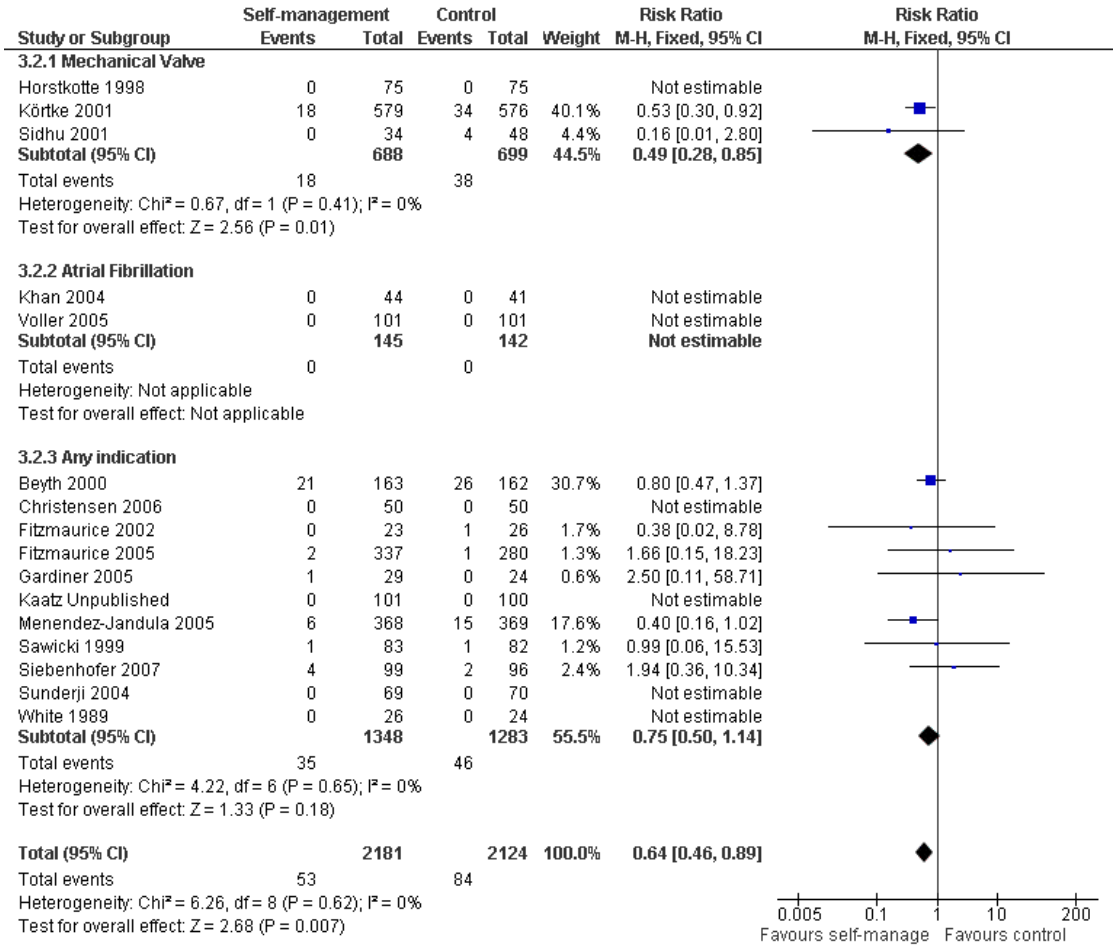


Figure 10. Forest plot of comparison: 3 Mortality, outcome: 3.3 Events by Self-adjustment (sensitivity).



Two studies (Khan 2004; Voller 2005) reported on patients with atrial fibrillation, no deaths were reported (Figure 11). A significant reduction in mortality occurred in patients who self-managed (Fitzmaurice 2002; Fitzmaurice 2005; Körtke 2001; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Siebenhofer 2007) compared to standard therapy (RR 0.55, 95% CI 0.36 to 0.84; P = 0.005). A non-significant effect was found for the self-monitoring only trials (Beyth 2000; Gardiner 2005) (RR 0.84, 95% CI 0.50 to 1.41; P = 0.51). The subgroup interaction was non-significant (P = 0.19). The post-hoc subgroup analysis for specialised care (RR 0.58, 95% CI 0.27 to 1.28) and family physician care (RR 0.30, 95% CI 0.30 to 0.63) showed only family physician care to be significant; however the subgroup interaction was not siginficant (P = 0.49).

Figure 11. Forest plot of comparison: 3 Mortality, outcome: 3.2 Events by Clinical Condition.



Major haemorrhage

Eighteen trials reported major haemorrhage outcomes (4723 participants, 172 events); 14 trials (15 groups) provided the information to calculate the overall effect size (Beyth 2000; Fitzmaurice 2002; Fitzmaurice 2005; Gadisseur 2003 Self mge; Horstkotte 1998; Kaatz Unpublished; Khan 2004; Körtke 2001; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Siebenhofer 2007; Sunderji 2004; Voller 2005). Compared to standard therapy, self-monitoring and self-management were associated with a non-significant reduction in major haemorrhage (RR 0.87, 95% CI 0.66 to 1.16; P = 0.34) (Figure 12). This result was stable to removal of the four studies deemed to be of low quality (RR 0.88, 95% CI 0.65 to 1.18; P = 0.39) (Figure 13). In terms of clinical condition, three studies (Horstkotte 1998; Körtke 2001; Sidhu 2001) included patients with mechanical valves only and two studies (Khan 2004; Voller 2005) reported on patients with atrial fibrillation. No significant differences were found.

Figure 12. Forest plot of comparison: 1 Major haemorrhage, outcome: 1.1 Events by Self-adjustment.

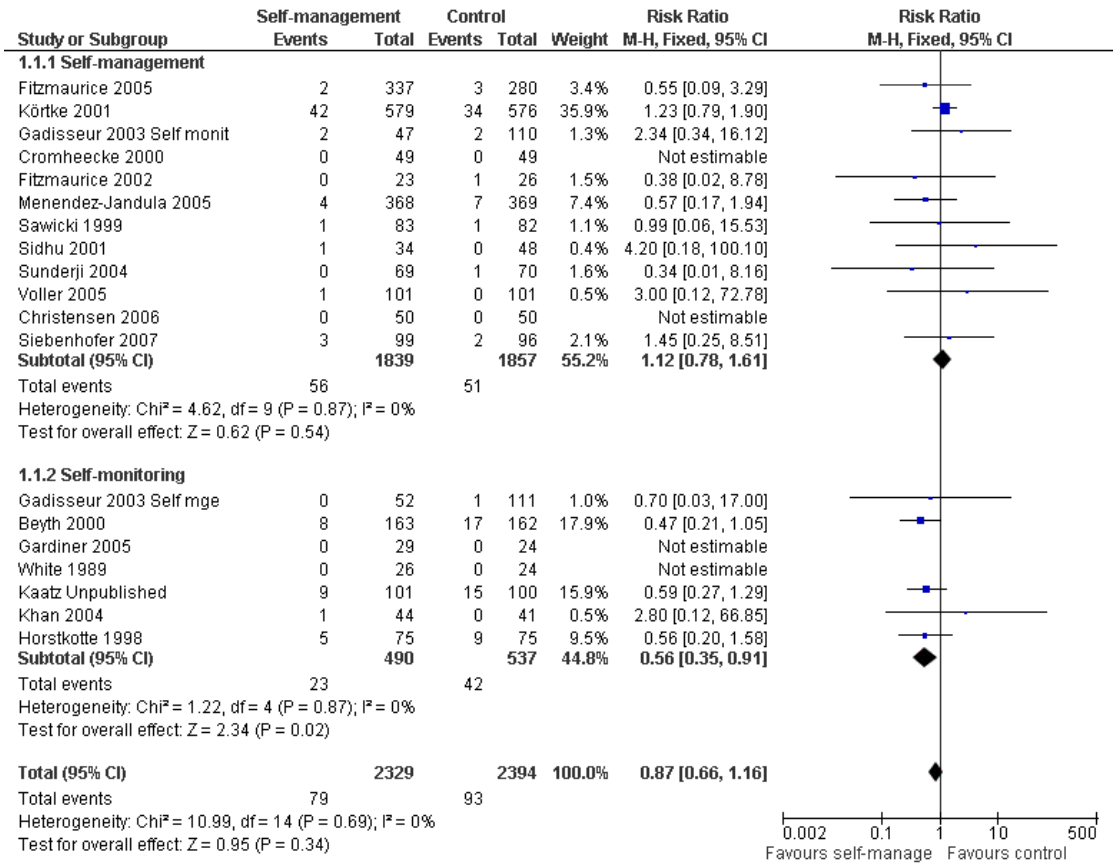
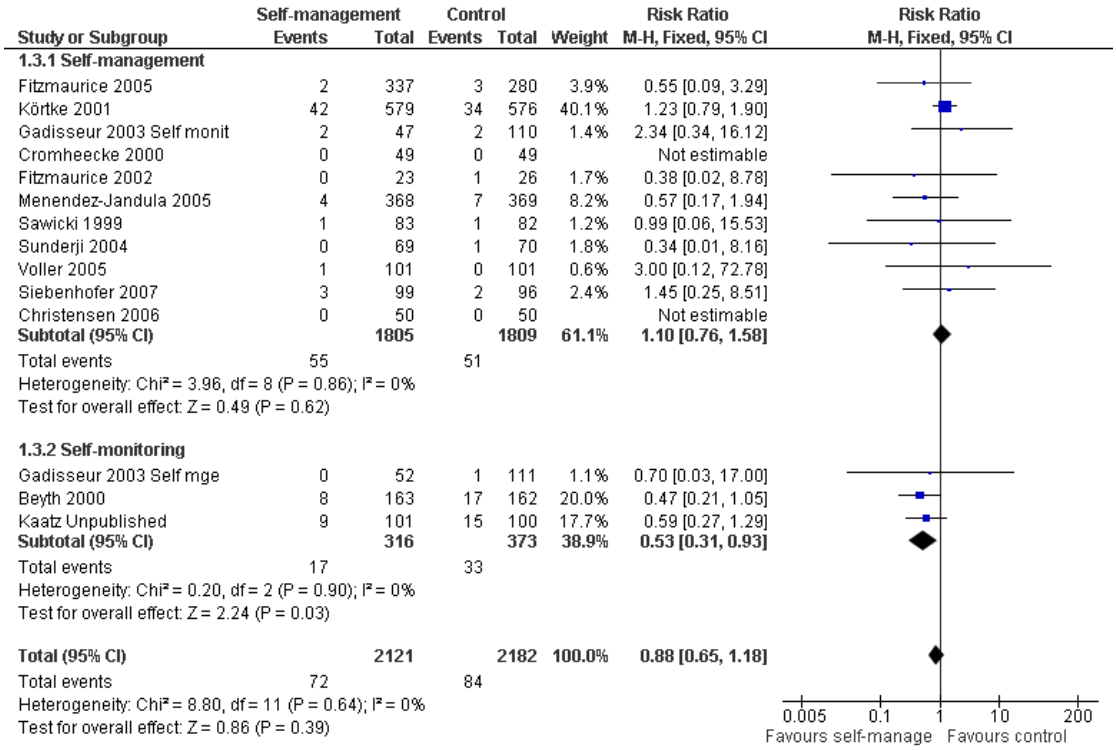
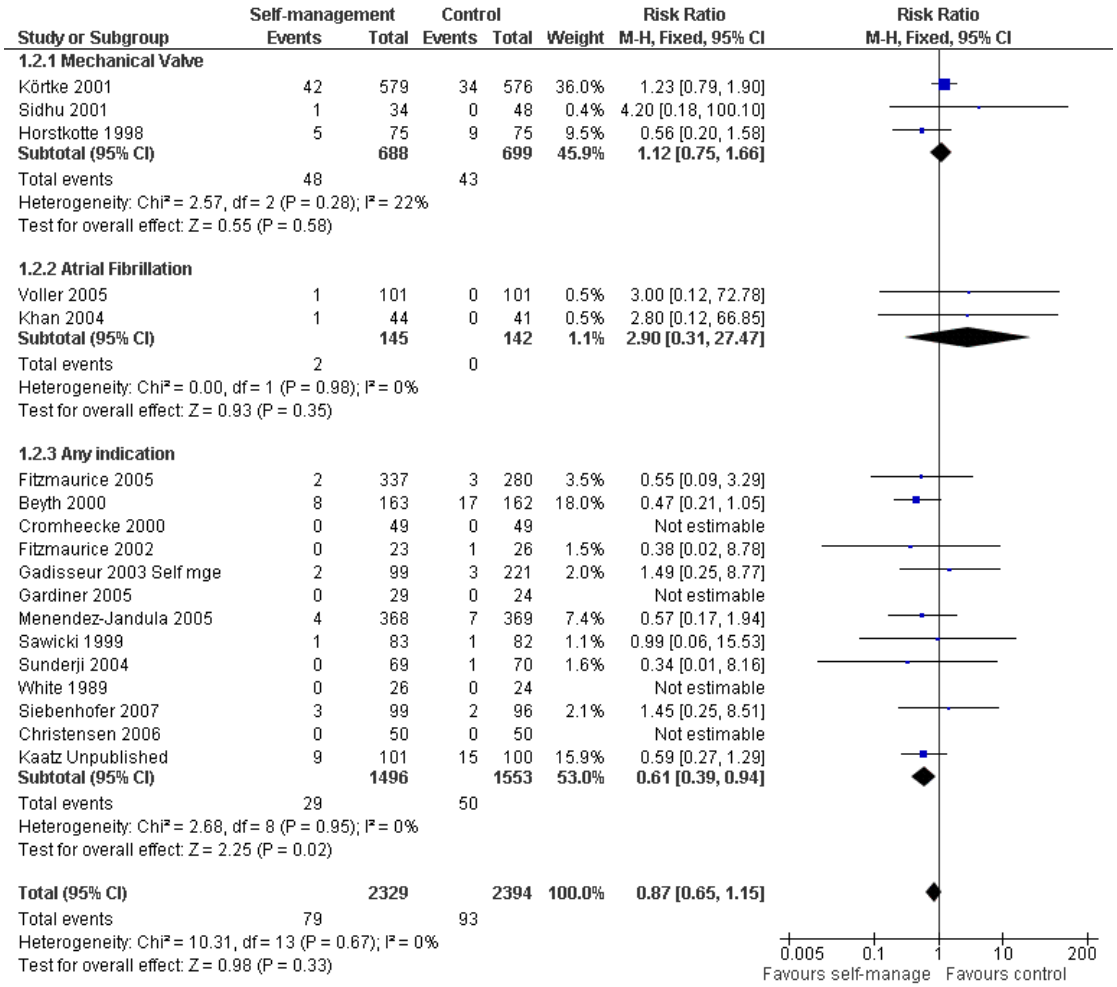


Figure 13. Forest plot of comparison: 1 Major haemorrhage, outcome: 1.3 Events by Self-adjustment (sensitivity).



The inability to distinguish between the two conditions in the remaining trials meant there was insufficient power to determine significance by clinical condition (Figure 14). In those who self-monitored (Beyth 2000; Gadisseur 2003 Self mge; Horstkotte 1998; Kaatz Unpublished; Khan 2004) a significant reduction in events occurred compared to standard therapy (RR 0.56, 95% CI, 0.35 to 0.91; P = 0.02). Self-management (Fitzmaurice 2002; Fitzmaurice 2005; Gadisseur 2003 Self monit; Körtke 2001; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Siebenhofer 2007; Sunderji 2004; Voller 2005) was comparible with standard therapy (RR 1.12, 95% CI 0.78 to 1.61; P = 0.54); the subgroup interaction for this outcome, between the two groups, was significant (P = 0.02). The post-hoc subgroup analysis for specialised care (RR 0.71, 95% CI 0.41 to 1.23; P = 0.17) and family physician care (RR 0.94, 95% CI 0.66 to 1.33) showed neither to be significant (subgroup interaction P = 0.64).

Figure 14. Forest plot of comparison: 1 Major haemorrhage, outcome: 1.2 Events by Clinical Condition.



Tests in range

Thirteen trials reported results of mean INR within target range (Cromheecke 2000; Fitzmaurice 2002; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Horstkotte 1998; Kaatz Unpublished; Körtke 2001; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Siebenhofer 2007; Sunderji 2004; Voller 2005; White 1989). All studies but one (Kaatz Unpublished) reported improvements in the self-monitoring and self-management groups; six were statistically significant (Horstkotte 1998; Körtke 2001; Menendez-Jandula 2005; Sidhu 2001; Voller 2005; White 1989). Pooling of the mean percentage of tests in range was not possible as information was collected in two different ways: as the percentage of overall tests in range (Cromheecke 2000; Fitzmaurice 2002; Horstkotte 1998; Körtke 2001; Sawicki 1999; Sidhu 2001; Sunderji 2004; Voller 2005; White 1989), and the percentage of tests for each individual in range (Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Menendez-Jandula 2005). Improvements ranged from 3% to 21%. Eleven trials reported the percentage time within range (Beyth 2000; Christensen 2006; Fitzmaurice 2002; Fitzmaurice 2005; Gardiner 2005; Kaatz Unpublished; Khan 2004; Menendez-Jandula 2005; Sidhu 2001; Siebenhofer 2007; Sunderji 2004). Three studies (Beyth 2000; Sidhu 2001; Siebenhofer 2007) reported a significant improvement in the time in therapeutic range in the self-monitoring and self-management groups (see additional tables, Table 1).

Table 1. Tests in range

	Mean INR within target range, %			TIme within range, %		
Source			P value			P value
White 1989	*68*	*87*	<.001	-	-	
Horstkotte 1998	*22.3*	*43.2*	<.001	-	-	
Sawicki 1999	*43.2*	*53*	.22	-	-	
Beyth 2000	-	-		32	56	<.001
Cromheecke 2000	*49*	*55*	.06	-	-	
Sidhu 2001	*58*	*67.60*	<.0001	63.8	76.5	<.0001
Fitzmaurice 2002	*66 (61-71)**	*72 (65-80)**	NS	77 (67-86)*	74 (67-81)*	NS
Gadisseur 2003 Self mge; Gadisseur 2003 Self monit	*61.3*	*65*	.14	-	-	
Gardiner 2005	-	-		64 (26)	61 (20)	NS
Kaatz Unpublished	*54.2*	*64.6*	<.05	66.9	63.5	[..2] 0.127
Sunderji 2004	*58.7 (5.8)***	*64.8 (5.9)***	.23	63.2 (5.8)**	71.8 (5.5)**	.14
Khan 2004	-	-		70.4 (24.5)**	71.1 (14.5)**	NS
Körtke 2001	*60.5*	*78.3*	<.001	-	-	
Voller 2005	*58.5 (19.8)***	*67.8 (17.6)***	.0061	-	-	
Menendez-Jandula 2005	*55.6 (19.6)***	*58.6% (14.3)***	.02	64.9 (19.9)	64.3 (14.3)	.2
Fitzmaurice 2005	-	-		68 (65.2-70.6)	70 (68.1-72.4)	NS
Christensen 2006, Denmark	-	-		68.9 (59.3-78.2)	78.7 (69.2-81.0)	NS
Siebenhofer 2007†, Austria	*57.1 (40.4-72.4)*	*72.4 (53.5-79.4)*	<.001	66.5 (47.1-81.5)	75.4 (59.4-85.0)	<.029

* 95% Confidence intervals
** Standard Deviations
† Used median not mean

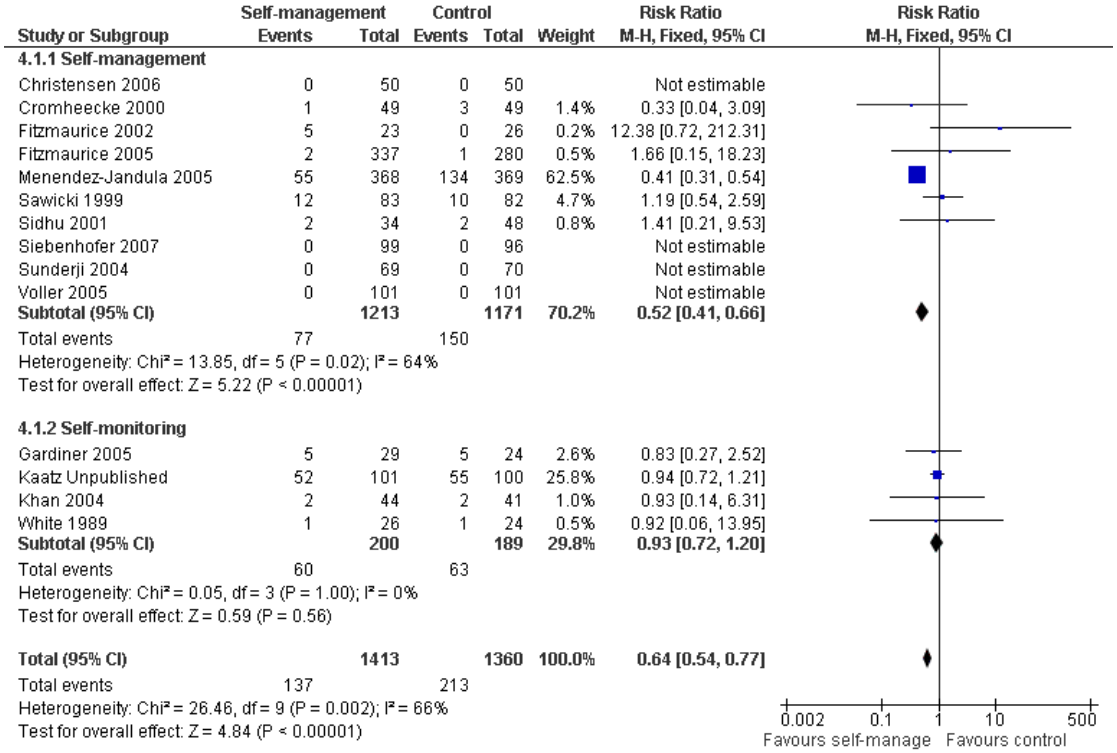
The method used to estimate the time within therapeutic INR target range in 11 studies was linear interpolation (Beyth 2000; Christensen 2006; Fitzmaurice 2002; Fitzmaurice 2005; Gardiner 2005; Kaatz Unpublished; Khan 2004; Menendez-Jandula 2005; Sidhu 2001; Siebenhofer 2007; Sunderji 2004).

Secondary endpoints

Minor haemorrhage

Fourteen trials reported minor haemorrhage outcomes, with 10 reporting events (2773 participants, 350 events) (Cromheecke 2000; Fitzmaurice 2002; Fitzmaurice 2005; Gardiner 2005; Kaatz Unpublished; Khan 2004; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; White 1989). Compared to standard therapy, self-monitoring and self-management resulted in a significant reduction in minor haemorrhage (RR 0.64, 95% CI 0.54 to 0.77; P < 0.00001) but results varied considerably (I^2 = 66%). One trial (Menendez-Jandula 2005) showed a significant effect on minor haemorrhage iwith self-management (RR 0.41, 95% CI 0.31 to 0.54) (Figure 15).

Figure 15. Forest plot of comparison: 4 Minor hemmorhage, outcome: 4.1 Events by Self-adjustment.



Frequency of testing

Ten studies reported on the total number of tests performed throughout the study (Fitzmaurice 2002; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Horstkotte 1998; Körtke 2001; Menendez-Jandula 2005; Sidhu 2001; Siebenhofer 2007; Sunderji 2004; Voller 2005; White 1989). Maximum test frequency oc-

curred in the study with the shortest duration (White 1989). The ratio of tests in the self-monitoring and self-management groups compared to the control groups ranged from 1.69 to 4.98; this ratio increased with duration of study (test for linear trend P < 0.002).

Feasibility of testing

A population of 11,738 was sampled in 14 trials (Beyth 2000; Christensen 2006; Fitzmaurice 2002; Fitzmaurice 2005; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Gardiner 2005; Khan 2004; Kaatz Unpublished; Körtke 2001; Menendez-Jandula 2005; Sawicki 1999; Sidhu 2001; Sunderji 2004; Siebenhofer 2007). Of that population, 7974 were either excluded or decided not to take part. The average proportion of people that could not (or would not) take part in the trials was 68% (range 31% to 88%). In trials which included older populations (Beyth 2000; Fitzmaurice 2005) the exclusion rates were much higher. Of the patients assigned to the intervention 24.9% (range 0% to 57.3%) were unable to complete self-monitoring or self-management. The main reasons for the drop-outs were: problems with the device, physical limitations preventing self-testing and problems with attending the training assessments or failing the assessment.

Other outcomes

Eight studies evaluated quality of life outcomes. These included ease of use (Gardiner 2005), anxiety caused by testing (Kaatz Unpublished), beliefs specific to warfarin (Khan 2004), and quality of life (Cromheecke 2000; Fitzmaurice 2002; Fitzmaurice 2005; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Khan 2004; Kaatz Unpublished; Sawicki 1999). Khan 2004 evaluated health status and quality of life using a validated tool, the 36-item United Kingdom Short Form Health Survey (UKSF-36) and the European Quality of Life questionnaire (Euroqol). Fitzmaurice 2002 used the individual quality of life (SEIQoL) tool for estimating quality of life and reported on results of patient interviews (Fitzmaurice 2005). Three trials (Cromheecke 2000; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Sawicki 1999) used a questionnaire designed by Sawicki on patients' feelings toward anticoagulation therapy. Three studies (Cromheecke 2000; Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Sawicki 1999) showed a significant difference in treatment satisfaction. In addition, one study (Gadisseur 2004) reported quality of life outcomes (Gadisseur 2003 Self mge; Gadisseur 2003 Self monit) showing greater treatment satisfaction in the self-monitoring group compared to the self-management group.

Optimal information size

The calculated optimal information size needed for a reliable and conclusive treatment effect was 5150 in each arm. This assumed a 2% thromboembolic event rate in the control group, a 50% RR reduction, a power of 95%, and a two-sided alpha = 0.01. The current meta-analysis has just over 2300 in each arm, which would give a 60% power using the same assumptions.

One of the main trials included in the meta-analysis showed a clear absence of correlation between the benefits observed and the degree of control (Menendez-Jandula 2005). We therefore questioned the influence of this study by performing a post hoc sensitivity analysis that removed the trial; the beneficial effects observed for all the major outcomes remained similar.

DISCUSSION

To our knowledge the present study is the most comprehensive review to date. The analysis provides new information in terms of individual outcomes and the limitations of self-monitoring or self-management. Our results need to be treated with some caution. Although self-monitoring or self-management of oral anticoagulation leads to a significant 50% reduction in thromboembolism and 13% reduction in major haemorrhage, the 36% reduction in mortality from all causes was largely influenced by one study. In those who used self-management therapy there appeared to be a greater reduction in thromboembolic events and mortality than with self-monitoring alone, but at a cost of less reduction in major haemorrhage. In addition, the applicability of self-monitoring and self-management is low and reluctance of suitable patients to participate in the trials was high.

This systematic review provides information additional to that in previously published reviews of self-monitoring or self-management of oral anticoagulation (Bazian 2005; Christensen 2007; de Solà-Morales 2005; Heneghan 2006a; Ødegaard 2004; Siebenhofer 2004). In addition we provide an analysis of the optimal sample size required for more reliable estimates. The main results of this review are consistent with previous reviews. The Christensen 2007 review of 10 trials showed that self-management was associated with a reduced risk of mortality (RR 0.48, 95% CI 0.29 to 0.79; P = 0.004) and major complications (RR 0.58, 95% CI 0.42 to 0.81; P = 0.001) with increased time being spent within the therapeutic INR target range (weighted mean difference 6.53, 95% CI 2.24 to 10.82; P = 0.003). Another review of eight trials (Ødegaard 2004) identified a significant reduction in major clinical events (OR 0.62, 95% CI 0.43 to 0.90; P < 0.01); a review of four trials (Siebenhofer 2004) concluded that patient self-management is safe and can improve the quality of anticoagulation control. A review of 12 trials (seven RCTs and five quasi-experimental trials) (de Solà-Morales 2005) reported no difference between patients undertaking self-management and those receiving usual care in the time spent in the therapeutic range and in the incidence of adverse effects. Bazian's review (which was less comprehensive) also did not show a difference between self-management and routine care (Bazian 2005).

This current review adds four trials (Fitzmaurice 2005, Siebenhofer 2007, Christensen 2006,Kaatz Unpublished) to those in our previous review (Heneghan 2006a). The results are broadly similar as this review showed significant reductions in thromboembolic events (odds ratio (OR) 045, 95% CI 030 to 068), all-cause mortality (OR 061, 038 to 098), and major haemorrhage (OR 065, 042 to 099). Trials of combined self-monitoring and self-management showed significant reductions in thromboembolic events (OR 027, 012 to 059) and death (OR 037, 016 to 085) but not major haemorrhage effects (OR 093, 042 to 205).

That patients who are capable of self-management therapy have fewer thromboembolic events and lower mortality at the expense of no reduction in major haemorrhage events compared with those who self-monitor alone is of interest. It would seem that patients who self-manage may deem a major haemorrhage less detrimental than a thrombotic event. This may occur if clinicians are more reluctant to risk a haemorrhagic event at the expense of a concommitant increase in thrombotic events. This explanation is hypothetical and can only be explored through the capture of individual patient data.

Intrinsic limitations to self-monitoring and self-management include the reluctance of individuals to participate in self-management and the extensive training required to do so. Self-monitoring is not feasible for up to half of the patients requiring anticoagulation. Factors influencing patient participation within trials included problems with the device; physical limitations; attending training sessions; or failing the assessment. An additional problem with adoption in clinical practice will be the relatively high cost of the test strips. The reliability of self-testing devices can affect test results; however, available devices give INR results which are comparable with those obtained in laboratory testing (Ansell 2005). Self-monitoring and self-management is also associated with a rate of testing that is higher than with usual care. In effect self-managed warfarin dosing is analogous to self-adjusted insulin dosing according to a pre-specified sliding scale (Ansell 1996). Such self-managed treatment has been practiced for years by people with diabeties (Ansell 1996) and the use of self-monitoring or self-management offers independence and freedom to travel for selected patients.

Our review has some potential limitations. First, our search was comprehensive making serious publication bias less likely but it remains a concern. Therefore the results may represent an overestimate of the true effect of treatment. Second, variability in the quality of care in the control groups can affect the rate of testing and hence the benefit and safety of standard anticoagulation monitoring. Specialist programmes may improve outcomes by the same mechanism as self-monitoring or self-management, that is improving the time in therapeutic range and lessening the frequency of adverse outcomes. However, our post hoc subgroup analysis did not verify this effect. A further modifying factor is education and training. The two trials in which patients consented to participate and received education alone had better results than did those patients allocated to routine care (Gadisseur 2003 Self mge; Gadisseur 2003 Self monit; Khan 2004). Third, for all the major outcomes of this review, limitations in the published reports led to an absence of information about the allocation concealment procedure or blinding. However, several authors were successfully contacted and the additional information that they provided generally raised the assessed quality of the trials. This finding is in agreement with recent empirical evidence suggesting that authors fail to report concealment of randomisation and blinding (Devereaux 2004). The limitations outlined above weaken the reported inferences concerning the effects of self-monitoring or self-management and led us to rate the quality of the evidence as moderate (GRADE 2008). Fourth, it was not possible to combine the proportion of tests in range nor determine the mean time in range and the rate of outlier values. To further understand the effects of self-monitoring and self-management on both the time in range and tests in range an individual patient data meta-analysis is required. Only one trial had a duration of over two years, though long-term benefits for self-management have been seen in a non-randomized study over five years (Sawicki 2003). Fifth, we applied the logic of early stopping of randomized controlled trials to determine whether our meta-analysis could be considered definitive (Montori 2005). From this we determined whether the evidence is adequate to recommend that no further studies are needed (Pogue 1997). The calculated optimal information size needed to reliably detect a plausible treatment effect was larger than the one we achieved (5150 versus 2300 patients per group).

Self-monitoring and self-management are likely to prevent thromboembolism to a greater extent than with standard monitoring. The mechanism of effect is probably through increasing the number of INR values in range and therefore the longer time that patients are in the therapeutic range. The observed reduction in mortality is likely to be related to the lower incidence of fatal thromboembolic events. Despite the limitations outlined above the apparent beneficial effects are large, and even smaller true underlying effects would probably justify widespread use of self-monitoring and self-management of oral anticoagulation in suitable candidates. Larger, better designed trials are necessary to definitively establish the magnitude of effect of this strategy; population-based observational studies can reflect real clinical practice.

AUTHORS' CONCLUSIONS

Implications for practice

Self-monitoring and self-management by patients can improve the quality of oral anticoagulation therapy compared to standard monitoring. The patients spend more time within the therapeutic range resulting in decreases in thromboembolic events and mortailty with no increase in harms. Nevertheless, results suggest the need for further trials to strengthen the robustness of conclusions

and the true extent of the observed effect. Further studies should explore components of the intervention that affect the feasibility of self-monitoring and self-management and identify means to improve uptake and effectiveness. Self-monitoring or self-management is potentially not feasible for half of the patients requiring anticoagulation. The costs of meters and test strips may prevent wide-scale uptake in low and middle income countries, where this intervention could have considerable benefit.

Implications for research

The moderate quality of the evidence, potential for biases, and the fact that the optimal information size has not been achieved means that there is a need for a large, pragmatic multicentre trial. Such trials should account for the potential confounding effects of education and the quality of the control group care. We are aware of a large study in the US which is due to be published in 2010 (Matchar 2005). We will update this review once the results from this study are published. To further explore important subgroup effects, we are undertaking an individual patient data meta-analysis of the identified studies. The results from this analysis will be available in 2010. In addition, for the results to be generalisable to the population at large, there is a need for population-based studies that collect data on adverse event rates, time in range, and factors that impinge on successful self-monitoring and self-management. The nature of this intervention lends itself to a registry to guarantee its safety and effectiveness in clinical practice. Future studies should set out to understand why people decide to use self-management (or not) and should incorporate consumer knowledge about self-management, triggers to seek care, self-efficacy or self-confidence to self-manage, and perceived or actual support.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Beyth 2000

Methods	Multicentre randomized controlled trial. Randomization was stratified according to baseline risk.
Participants	The study enrolled 325 hospitalized patients, mean age 75 years, who were receiving intravenous heparin every 24 hours. The study was based in several university hospitals (Cleveland).
Interventions	**Self-monitoring** The intervention group (n=163) used home self-testing using Coumatrak Protime Test System ® to self-monitor prothrombin time. 1-hour education session, patients phoned results to coach who made recommendations. The conventional management group (n=162) received medical care including management, dosing and medical information managed by primary care physician as per usual care. Duration of the study 6 months. Oral anticoagulant used: warfarin.
Outcomes	Percentage time within target range. Complications including major bleeding, thromboembolic and mortality.
Notes	One to one teaching. Training lasted 30 min to 1 hour. Patients instructed to check prothrombin 3 times in the first week after hospital discharge and weekly in the first month, and monthly thereafter depending on the results. 100% up at 6 months.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomization stated to have been done but no method reported.
Allocation concealment?	Yes	Clearly adequate concealment.
Intention to treat analysis?	Yes	
Reporting of losses of follow-up?	Unclear	<20% losses to follow up.
Blinding?	Yes	Blinded data collectors.

Christensen 2006

Methods	Single centre randomized controlled trial.
Participants	The study enrolled 100 ambulatory patients. Mean age 63 years intervention group mean age 69 years control group. Oral anticoagulation therapy for at least 8 months. The study was based in

Christensen 2006 (*Continued*)

	the Center of Self-managed Oral Anticoagulation (Denmark).
Interventions	**Self-management** The intervention group (n=50) receive self-management using Coaguchek® to measure INR once a week and these results were used by the patient to adjust the coumarin dosage. The conventional management group (n=50) received at least monthly blood sampling either at the hospital laboratory nearest the patient's home or with a coagulometer at a physician's office. These results were used to adjust the coumarin dosage. Duration of the study 6 months. Oral anticoagulant used: coumarin.
Outcomes	Major bleeding. Thromboembolism. Mortality. Variance of INR value. Time within therapeutic INR target range. Composite end point.
Notes	No formal training. The patient assumed gradually management and self adjustment with monitoring. After 27 weeks there was a formal examination.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computerized randomization schedule.
Allocation concealment?	Yes	
Intention to treat analysis?	Yes	
Reporting of losses of follow-up?	Yes	10% of patients were lost to follow up.

Cromheecke 2000

Methods	Single centre randomized controlled crossover trial. Allocation concealment by sealed envelopes. No washout period.
Participants	The study enrolled 50 consecutive outpatients, mean age 42 years, who were receiving long-term anticoagulation (phenprocoumon or acenocumarol). The study was based in the departments of cardiology and internal medicine of the Academic Medical Centre (Amsterdam).
Interventions	**Self-management** The intervention group used home self-testing using Coaguchek® to self-monitor prothrombin time and self-dosing testing performed once a week. The conventional management was done by the anticoagulation clinic. After three months patients crossed over the alternative management strategy. Duration of the study 3 months. Oral anticoagulant used: acenocoumarol 65% patients, phenprocoumon 35% patients.

Cromheecke 2000 (*Continued*)

Outcomes	Major bleeding, minor bleeding, thromboembolism, mortality. Number of measurements within 0.5 INR units from target INR. Percentage INR within target range. Percentage under/over anticoagulation.
Notes	All patients were educated and trained to self-manage anticoagulation during a structured educational program of two 2 hours sessions. None (0%) losses to follow up.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	Sealed envelopes.
Intention to treat analysis?	No	
Reporting of losses of follow-up?	Yes	
Blinding?	Yes	Blinded outcome assessors.

Fitzmaurice 2002

Methods	Multicentre randomized controlled trial. Randomization by computer generated coding.
Participants	The study enrolled 56 ambulatory patients (most receiving warfarin for atrial fibrillation). Mean age 63 years self-management mean age 69 years control group. The study was based in six general practices in the west Midlands using the Birmingham model of anticoagulation management.
Interventions	**Self-management** The intervention group (n=30) used self-testing and self-dosing using Coaguchek® device to self-monitor INR. Testing was performed every 2 weeks or after 1 week following dosage adjustment. Conventional management group (n=26) received routine care in practice clinics. Follow up six months. Duration of the study 6 months. Oral anticoagulant used: warfarin.
Outcomes	Haemorrhage (minor and serious adverse events). Quality of life. Percentage of time in range. Proportion of time in range. Cost analysis.
Notes	Intervention group atended two 1-2 hours workshops. Workshops were based within individual practices, were organised by research staff and attended by practice staff.

Risk of bias

Item	Authors' judgement	Description

Fitzmaurice 2002 (*Continued*)

Adequate sequence generation?	Yes	Computer generated coding.
Allocation concealment?	Yes	
Intention to treat analysis?	No	
Reporting of losses of follow-up?	Yes	12.5% of patients were lost to follow up.

Fitzmaurice 2005

Methods	Multicentre randomized controlled trial.
Participants	The study enrolled 617 ambulatory patients, mean age 69 years, who were receiving long-term anticoagulation (warfarin). The study was based in primary care centres within Midlands Research Consortium (United Kingdom).
Interventions	**Self-management** The intervention group (n=337) used home self-testing using Coaguchek® managed anticoagulation for 12 months, testing INR very two weeks (one week after a dose change). Adjusted dosage by using a laminated dosing schedule. The control group (n=280) used hospital or practice based anticoagulant clinics. Duration of the study 12 months. Oral anticoagulant used: warfarin.
Outcomes	Major and miror haemorrhage. Thromboembolism. Percentage of time within therapeutic range.
Notes	Randomized allocation to intervention or routine care. Trained anticoagulation nurses gave patients training at the practice. After the training, patients considered capable of doing self management were given home testing equipment Coaguchek® managed anticoagulation for 12 months, testing INR very two weeks (one week after a dose change). Adjusted dosage by using a laminated dosing schedule.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	Central telephone randomization.
Intention to treat analysis?	Yes	
Reporting of losses of follow-up?	Unclear	Inadequate report or >20% losses (41.5% losses to follow up).
Blinding?	Yes	Blinded outcome assessors.

Gadisseur 2003 Self mge

Methods	Single centre randomized controlled trial. Randomization to groups (A,B,C,D) followed a 2-step partial Zelen-design.
Participants	The study enrolled 320 patients. Mean age 57 years who were receiving long term anticoagulation. The study was based in two Dutch anticoagulation clinics.
Interventions	**Self-monitoring** Group A (n=52) used self-testing using Coagucheck® monitoring device. Group B (n=47) used self-testing using Coagucheck® and self-dosing. Group C (n=60) received education alone and routine care. Group D (n=161) received only routine care. Duration of the study 6.5 months. Oral anticoagulant used: phenprocoumon 70% patients / acenocoumarol 30% patients.
Outcomes	Major and minor bleeding. Major non-fatal thromboembolism and mortality. Dosage correction, percentage of time in range, quality of OAT.
Notes	Groups A, B and C received the same training (three sessions of 90-120 min).

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated list.
Allocation concealment?	Yes	
Intention to treat analysis?	No	
Reporting of losses of follow-up?	Yes	8.2% of patients were lost to follow up.
Blinding?	Yes	Blinded health care providers.

Gadisseur 2003 Self monit

Methods	Single centre randomized controlled trial. Randomization to groups (A,B,C,D) followed a 2-step partial Zelen-design.
Participants	The study enrolled 320 patients. Mean age 57 years who were receiving long term anticoagulation. The study was based in two Dutch anticoagulation clinics.
Interventions	**Self-management** Group A (n=52) used self-testing using Coagucheck® monitoring device. Group B (n=47) used self-testing using Coagucheck® and self-dosing. Group C (n=60) received education alone and routine care. Group D (n=161) received only routine care. Duration of the study 6.5 months. Oral anticoagulant used: phenprocoumon 70% patients, acenocoumarol 30% patients.

Gadisseur 2003 Self monit (*Continued*)

Outcomes	Major and minor bleeding. Major non-fatal thromboembolism and mortality. Dosage correction, percentage of time in range, quality of OAT.
Notes	Groups A, B and C received the same training (three sessions of 90-120 min).

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated list.
Allocation concealment?	Yes	
Intention to treat analysis?	No	
Reporting of losses of follow-up?	Yes	8.2% of patients were lost to follow up.
Blinding?	Yes	Blinded healthcare providers.

Gardiner 2005

Methods	Single centre randomized controlled trial.
Participants	The study enrolled 84 patients, mean age 58 years, receiving long term anticoagulation. The study was based in an anticoagulation clinic in University Hospital (London).
Interventions	Self-monitoring The intervention group (n=44) used home self-testing using the Coagucheck® monitoring device. The conventional management group (n=40) received usual care by anticoagulant clinic visiting the hospital for testing every 4 weeks. Duration of the study 6 months. Oral anticoagulant used: not reported.
Outcomes	Major and minor bleeding. Thromboembolism and mortality. Percentage of time within target range. Acceptability.
Notes	The intervention group attended two training sessions.

Risk of bias

Item	Authors' judgement	Description
Intention to treat analysis?	No	
Reporting of losses of follow-up?	Yes	23.8% of patients were lost to follow up.

Horstkotte 1998

Methods	Unicentric randomised controlled trial.
Participants	The study enrolled 150 patients. Outpatients with isolated aortic or mitral valve replacement.
Interventions	**Self-monitoring** The intervention group (n=75) used home self-testing measuring INR twice a week and contacted coagulation clinic by phone. The conventional management group (n=75) was managed by home physician. Duration of the study not reported. Oral anticoagulant used: not reported.
Outcomes	Major haemorrhage, thromboembolic events, mortality.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Possibly adequate or not used.
Intention to treat analysis?	Yes	
Reporting of losses of follow-up?	Yes	1.3% losses to follow up.

Kaatz Unpublished

Methods	Multicentre randomized controlled trial.
Participants	The study enrolled 201 patients. Receiving long term anticoagulation. The study was based in three anticoagulation clinics.
Interventions	**Self-monitoring** The intervention group (n=101) used home self-testing using the Coagucheck® monitoring device. The conventional management group (n=100) received usual care (point of care testing). Duration of the study not reported. Oral anticoagulant used: warfarin.
Outcomes	Major and minor bleeding. Thromboembolic. Percentage of time in the therapeutic range. Convenience, satisfaction and worry.
Notes	Patients were trained to use Coagucheck®. Training by anticoagulation clinic research nurse. None patients were lost to follow-up.

Risk of bias

Item	Authors' judgement	Description

Kaatz Unpublished (*Continued*)

Adequate sequence generation?	Yes	Random sequence was generated using variable block sizes and stratification.
Allocation concealment?	Yes	Sealed opaque envelopes.
Intention to treat analysis?	Yes	
Reporting of losses of follow-up?	Yes	None (0%) patients were lost to follow up.

Khan 2004

Methods	Single centre randomized controlled trial.
Participants	The study enrolled 125 patients, mean age 73 years, receiving oral anticoagulation for atrial fibrillation. The study was based in an anticoagulation service university (Newcastle).
Interventions	Self-monitoring. Group A (n=44) used home weekly self-testing using the Coagucheck® monitoring device. Group B (n=41) received education alone and clinical care. Group C (n=40) received usual care. Duration of the study 6 months. Oral anticoagulant used: warfarin.
Outcomes	Major and minor bleeding. Non fatal thromboembolism. Mortality. Percentage of time within target range. Change in the SD of the INR. Dose changes. Quality of life.
Notes	Groups A and B received one training session (2h) attended in groups of 2-3 people. Sessions were based on educational materials and led by a doctor, 4.8% of patients were lost to follow up.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random numbers table, computer-generated program.
Allocation concealment?	Unclear	Possibly adequate or not used.
Intention to treat analysis?	No	
Reporting of losses of follow-up?	Yes	9.1% losses to follow up.

Körtke 2001

Methods	Single centre randomized controlled trial.
Participants	The study enrolled 600 patients, mean age 62.5 years, receiving permanent oral anticoagulation due to mechanical heart valve replacement. Based in the department of thoracic and cardiovascular surgery (Germany).
Interventions	**Self-management** The intervention group (n=305) used home self-testing initially using Biotrack, later renamed Coagucheck® plus. The control group (n=295) used outpatient cardiologic check up and coagulation controls every 6 months. Unclear if self-dosing too. Duration of the study ≤ 51 months. Oral anticoagulant used: phenprocoumon.
Outcomes	Major and minor bleeding. Major non fatal thromboembolism. Mortality. Percentage of INR within therapeutic range.
Notes	No details about training.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Intention to treat analysis?	No	
Reporting of losses of follow-up?	Yes	8.3% of patients were lost to follow up.

Menendez-Jandula 2005

Methods	Single centre randomized controlled trial.
Participants	The study enrolled 737 ambulatory patients, mean age 66 years, who were receiving long-term therapy before the study for at least 3 months (acenocoumarol). The study was based in a University Hospital (Barcelona, Spain).
Interventions	**Self-management** The intervention group (n=368) used home self-testing using the Coagucheck® and self-dosing. Patients in the self-management group determined the appropriate dose of oral anticoagulant and the time of the next INR test. The conventional management group (n=369) visited the hospital for every four weeks to check their INR. Duration of the study up to 17 months. Oral anticoagulant used:(warfarin or acenocoumarol) proprtions not reported

Menendez-Jandula 2005 (*Continued*)

Outcomes	Major and minor haemorrhage. Thromboembolic. Mortality. Percentage of INR within target range. Time within target range.
Notes	Training: two 2-hour sessions in consecutive days run by a trained nurse.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Centralized telephone randomization.
Allocation concealment?	Yes	The sequence of randomization was concealed until the patient was assigned to a group.
Intention to treat analysis?	Yes	
Reporting of losses of follow-up?	Unclear	11.9% of patients were lost to follow-up.
Blinding?	Yes	Blinded outcome assessors.

Sawicki 1999

Methods	Multicentre randomized study.
Participants	The study enrolled 179 patients, mean age 55 years, receiving long term oral anticoagulation. The study was based in 5 referral centres (Germany).
Interventions	**Self-management** The intervention group (n=90) used home self-testing and self-dosing the Coagucheck® monitor, measuring INR 1-2 times per week and adjusted their anticoagulant according to their INR values. Patients recorded INR values routinely, recorded the results and anticoagulation dosages in their logbook. The conventional management group (n=89) visited twice monthly. Adjustment by general practitioner. Duration of the study 6 months. Oral anticoagulant used: phenprocoumon.
Outcomes	Major and minor bleeding. Non fatal thromboembolism. Mortality. INR within target range.
Notes	Structured educational program, three consecutive weekly teaching sessions of 60-90 minutes.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer program.

Sawicki 1999 (*Continued*)

Allocation concealment?	Unclear	Possibly adequate or not used.
Intention to treat analysis?	Yes	
Reporting of losses of follow-up?	Yes	7.8% of patients were lost to follow up.
Blinding?	Yes	Blinded data collectors.

Sidhu 2001

Methods	Single centre randomized controlled trial.
Participants	The study enrolled 100 patients, mean age 61 years, with a heart valve operation and less than 85 years. Life long anticoagulation.
Interventions	**Self-management** The intervention group (n=51) received home self-testing using the Coagucheck® and self-dosing. INR testing performed once a week, patients were encouraged to perform more frequent INR measurements if they were necessary. They adjusted their anticoagulant dosageaccording to a protocol. Patients recorded the results of their INR measurements in a standard book. The conventional management group (n=49) used hospital anticoagulant clinic or family physician care. Duration of the study 24 months. Oral anticoagulant used: warfarin.
Outcomes	Minor bleeding. Minor thromboembolic. Mortality. Time within target range. Percentage of values within target range.
Notes	Training: two 3-hour sessions (groups of 2-5 patients).

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Simple random number generator program.
Allocation concealment?	Unclear	Possibly adequate or not used.
Intention to treat analysis?	No	
Reporting of losses of follow-up?	Unclear	33.3% of patients were lost to follow up in intervention group and 2% in the conventional management group.

Siebenhofer 2007

Methods	Multicentre randomized controlled trial.
Participants	The study enrolled 195 patients, mean age 69 years, with indication of long term oral anticoagulation. The study was based in 3 departments specializing in the treatment of patients receiving long-term oral anticoagulation therapy (Austria).
Interventions	**Self-management** The intervention group (n=99) received home self-testing using the Coagucheck® and self-dosing. INR testing performed once a week, adjust anticoagulant dosage accordingly, and to contact the training centre in case of difficulties. The control group (n=96) anticoagulant dosage by usual attending physicians in general practice or at a hospital based specialised anticoagulation clinic. Duration of the study 12 months. Oral anticoagulant used: phenprocoumon 90% patients, acenocoumarol 10% patients.
Outcomes	Major bleeding. Thromboembolic. Mortality. (Composite endpoint). INR values.
Notes	Patients assigned to the control group participated in a single 90-miute session including basic theoretical information. Patients assigned to intervention group participated in four consecutive weekly instruction sessions of 90 to 120 minutes each, in groups of three to six patients.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-based system.
Allocation concealment?	Yes	Allocation was done by a central statistical office by fax and without awareness of subject data. The sequence of randomisation was concealed until the patient was assigned to a group.
Intention to treat analysis?	Yes	
Reporting of losses of follow-up?	Yes	
Blinding?	Yes	Blinded outcome assessors.

Sunderji 2004

Methods	Single centre randomized controlled trial.
Participants	The study enrolled 139 patients, mean age 60 years, receiving warfarin for at least one month before randomization. Selected patients for study inclusion based on their assessment of competency, compliance and willingness to manage their own therapy. Based in a tertiary care setting or by referral as an outpatient at the University of British Colombia (Canada).

Sunderji 2004 (*Continued*)

Interventions	**Self-management** The intervention group (n=69) received home self-testing using Protime microcoagulation system and self-dosing determining the appropriate dose of oral anticoagulant and the time of the next INR test using a nomogram recording INR results and warfarin doses in a pocket calendar. The conventional management group (n=70) used primary care physician as per usual care. Duration of the study up to 8 months. Oral anticoagulant used: warfarin.
Outcomes	Major and minor haemorrhage. Thromboembolic. Mortality. Percentage INR within target range.
Notes	In a first 2-3h visit patients received education from a pharmacist. Participants were discharged to enable practice self-testing at home. In the second visit (1-2h) patients were required to demonstrate competency in self-testing and self-dosing.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomization code.
Allocation concealment?	Yes	Randomization code concealed.
Intention to treat analysis?	Yes	
Reporting of losses of follow-up?	Yes	10% of patients were lost to follow up.

Voller 2005

Methods	Multicentre randomized controlled trial.
Participants	The study enrolled 202 patients, mean age 64 years, with permanent non-valvular atrial fibrillation in long term anticoagulation. The study was based in 33 centres (Germany).
Interventions	**Self-management** Self testing using the Coagucheck® and self dosing (regime not reported). Usual care by family doctors (regime not reported). Duration of the study up to 19 months. Oral anticoagulant used: not reported
Outcomes	Percentage of INR within therapeutic range. Days within range. Complications.
Notes	Stopped early trial due to low number of events.

Risk of bias

Item	Authors' judgement	Description

Voller 2005 (*Continued*)

Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Intention to treat analysis?	No	
Reporting of losses of follow-up?	Unclear	19.8% drop-out.

White 1989

Methods	Single centre randomized controlled trial.
Participants	The study enrolled 50 patients started on warfarin for the first time with and unstable prothrombin ratio. Home monitor mean age 50±14 years. Anticoagulation clinic group 49±16 years.
Interventions	**Self-monitoring** The intervention group (n=26) used the home monitor Coumatrak (managed by general internist) with a phone contact management to testing prothrombin time. The conventional management group (n=24) visited specialized anticoagulation clinic (registered nurses specialists). Duration of the study 2 months. Oral anticoagulant used: warfarin.
Outcomes	Major and minor bleeding. Thromboembolism. Percentage of time within the target range. Median % time in the therapeutic range. Number of prothrombin tests. Compliance.
Notes	Patients were trained to use the monitor and had to be able to determine at least on prothrombin time successful.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Unclear	Possibly adequate or not used.
Intention to treat analysis?	No	
Reporting of losses of follow-up?	Yes	4.1% of patients in intervention group and 11.5% of patients in control group lost to follow up.

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

Christensen 2001	Non-randomized trial.
Christensen 2003	Comparative. Non-clinical trial.
Hambleton 2003	Non clinical trial.
Hasenkam 1997	Comparative. Non-clinical trial.
Hasenkam 1998	Comparative. Non-clinical trial.
Heidinger 2000	Non-randomized trial.
Horstkotte 2004	Non-comparative study.
Lafata 2000	Comparative. Non-clinical trial.
Leger 2004	Non-comparative study.
Levi 2001	Non-comparative study.
Piso 2002	Clinical trial. Only one comparative arm.
Rosengart 2002	Non-clinical trial.
Schmidtke 2001	Non-randomized trial.
Sunderji 2005	Non-evaluated intervention of interest.
Watzke 2000	Non randomized study.

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

Matchar 2005

Trial name or title	The Home INR Study (THINRS)
Methods	
Participants	
Interventions	
Outcomes	
Starting date	

Matchar 2005 (*Continued*)

Contact information	David B. Matchar, MD, Duke University Medical Center, Center for Clinical Health Policy Research, 2200 W Main St, Suite 220, Durham, NC
Notes	

DATA AND ANALYSES

Comparison 1. Major haemorrhage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Events by Self-management	19	4723	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.66, 1.16]
1.1 Self-management	12	3696	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.78, 1.61]
1.2 Self-monitoring	7	1027	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.35, 0.91]
2 Events by Clinical Condition	18	4723	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.65, 1.15]
2.1 Mechanical Valve	3	1387	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.75, 1.66]
2.2 Atrial Fibrillation	2	287	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [0.31, 27.47]
2.3 Any indication	13	3049	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.39, 0.94]
3 Events by Self-management (sensitivity)	14	4303	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.65, 1.18]
3.1 Self-management	11	3614	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.76, 1.58]
3.2 Self-monitoring	3	689	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.31, 0.93]

Comparison 2. Thromboembolic events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Events by Self-management	19	4723	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.36, 0.69]
1.1 Self-management	12	3696	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.31, 0.70]
1.2 Self-monitoring	7	1027	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.32, 1.00]
2 Events by Clinical Condition	18	4723	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.36, 0.69]
2.1 Mechanical Valve	3	1387	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.30, 0.91]
2.2 Atrial Fibrillation	2	287	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.09]
2.3 Any indication	13	3049	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.32, 0.74]
3 Events by Self-management (sensitivity)	15	4453	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.35, 0.68]
3.1 Self-management	11	3614	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.30, 0.68]
3.2 Self-monitoring	4	839	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.33, 1.03]

Comparison 3. Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Events by Self-management	16	4305	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.89]
1.1 Self-management	10	3441	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.36, 0.84]
1.2 Self-monitoring	6	864	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.50, 1.41]
2 Events by Clinical Condition	16	4305	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.89]
2.1 Mechanical Valve	3	1387	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.28, 0.85]
2.2 Atrial Fibrillation	2	287	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Any indication	11	2631	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.50, 1.14]
3 Events by Self-management (sensitivity)	12	4035	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.46, 0.90]
3.1 Self-management	9	3359	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.37, 0.88]
3.2 Self-monitoring	3	676	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.47, 1.37]

Comparison 4. Minor haemorrhage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Events by Self-management	14	2773	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.54, 0.77]
1.1 Self-management	10	2384	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.41, 0.66]
1.2 Self-monitoring	4	389	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.20]

HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 4, 2010

CONTRIBUTIONS OF AUTHORS

JM Garcia-Alamino, P Alonso-Coello, C Heneghan, and R Perera had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JM Garcia-Alamino organised the study concept and design. JM Garcia-Alamino, P Alonso-Coello, C Heneghan, A Ward, and D Fitzmaurice acquired the data. C Heneghan, JM Garcia-Alamino, R Perera, P Alonso-Coello, A Ward, and C Bankead analysed and interpreted the data. C Heneghan, A Ward, R Perera, JM Garcia-Alamino, P Alonso-Coello, and D Fitzmaurice drafted the manuscript. Statistical analysis was done by R Perera, C Heneghan, C Bankhead, and JM Garcia-Alamino. All authors approved the final manuscript. The authors were responsible for the search strategies and performing all searches for this review.

DECLARATIONS OF INTEREST

None known

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- Hospital de la Santa Creu i Sant Pau, Spain.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes were introduced between protocol and review stage to increase the scope and quality of the review. The title changed from "Self management for oral anticoagulation" to "Self-monitoring and self-management of oral anticoagulation". The authors changed from Garcia-Alamino JM, Martin JLR, Subirana M, Gich I to Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D, Heneghan C. The type of studies changed from "Randomized controlled trials assessing the therapeutic efficacy and safety of self-management" to "Randomized controlled trials assessing the therapeutic effectiveness and safety of self-monitoring or self-management of oral anticoagulation". In the 'Types of outcome measures' mortality was added as an outcome. The quality assessment of the studies in the review now includes assessment of the evidence with the GRADE system.