Self-monitoring of oral anticoagulation: a systematic review and meta-analysis

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Summary

Background **Near-patient testing has made self-monitoring of anticoagulation with warfarin feasible, and several trials have suggested that such monitoring might be equal to or better than standard monitoring. We did a systematic review and meta-analysis of all randomised controlled trials that assessed the effects of self-monitoring or self-management (self-testing and self-dosage) of anticoagulation compared with standard monitoring.**

Methods **We searched the Cochrane Register of Controlled Trials, MEDLINE, EMBASE to April 2005, and contacted manufacturers and authors of relevant studies. Outcomes analysed were: major haemorrhage, thromboembolic events, death, tests in range, minor haemorrhage, frequency of testing, and feasibility of self-monitoring.**

Findings **We identified 14 randomised trials of self-monitoring: pooled estimates showed significant reductions in thromboembolic events (odds ratio 0·45, 95% CI 0·30–0·68), all-cause mortality (0·61, 0·38–0·98), and major haemorrhage (0·65, 0·42–0·99). Trials of combined self-monitoring and self-adjusted therapy showed significant reductions in thromboembolic events (0·27, 0·12–0·59) and death (0·37, 0·16–0·85), but not major haemorrhage (0·93, 0·42–2·05). No difference was noted in minor haemorrhage. 11 trials reported improvements in the mean proportion of international normalisation ratios in range.**

Interpretation **Self-management improves the quality of oral anticoagulation. Patients capable of self-monitoring and self-adjusting therapy have fewer thromboembolic events and lower mortality than those who self-monitor alone. However, self-monitoring is not feasible for all patients, and requires identification and education of suitable candidates.**

Introduction

Oral anticoagulation with vitamin K antagonists clearly reduces thromboembolic events.[1–6] In particular, well-controlled anticoagulation with warfarin could potentially prevent more than half the strokes related to atrial fibrillation and to heart-valve replacements, with a low risk of major bleeding complications.[7] However, much of this potential benefit is still not realised because anticoagulation is either not done or not done well.

The therapeutic range for anticoagulants is narrow: an international normalised ratio (INR) of less than 2 increases the risk of thromboembolism, and an INR of more than 4·5 increases the risk of major bleeding.[8–10] To maintain the INR within this narrow target range requires frequent testing and appropriate adjustment. When monitored monthly, around 50% of patients remain within target range,[11] compared with 85% when monitored weekly.[12] Numerous barriers to the use of warfarin exist, including the complex pharmacokinetics of warfarin, the need for continuous monitoring and dose adjustments, bleeding events, non-compliance, drug interactions, and increased costs of monitoring and therapy.[7]

One way to improve anticoagulation management is the use of home testing devices that allow the patient to measure INR with a drop of whole blood.[13] Such hand-held devices have proved sufficiently reliable.[14,15] When self-monitoring, the patient can either self-test and self-adjust treatment according to a predetermined dose-schedule, or self-test and call a clinic to receive the appropriate dose adjustment. Potential advantages of self-monitoring include improved convenience for patients, better treatment compliance, more frequent monitoring, and fewer thromboembolic and haemorrhagic complications.[16] Self-monitoring of anticoagulation seems a credible alternative to existing models of care, although published guidelines state that there are no reliable clinical-outcome data in any of the published studies to lend support to its use.[17]

We aimed to assess the current evidence for the effectiveness of self-monitoring and self-adjustment by patients on treatment with oral anticoagulation.

Methods

Eligibility and search strategy

We included all published and unpublished controlled trials that: randomly assigned patients; compared the effects of self-monitoring (self-testing) or self-management (self-testing and self-dosage) of anticoagulation with control and dosage by personal physician, anticoagulation management clinics, or managed services; or reported the clinical outcomes of thromboembolic events and major bleeding episodes. We included studies of adults and children on anticoagulant therapy irrespective of the indication for treatment (eg, valve replacement, venous thromboembolism, atrial fibrillation). There were no language restrictions.

We searched Ovid versions of EMBASE (1980–2005) and MEDLINE (1966–2005), limiting our searches to randomised-controlled trials using a maximally sensitive strategy.[18] We modified these searches for the Cochrane Central Register of Controlled Trials, the Cochrane Library, issue 2, 2005, and Cinahl (1982–2005). MeSH terms used were "anticoagulants", "vitamin-K" OR "coumarins" AND "self-Care" "self-administration" OR "consumer-participation". We also searched for ongoing trials (eg, UK National Research Register and Trials Central), and hand-searched reference lists of all retrieved papers. We sought additional trials from field manufacturers of prothrombin time and INR monitors and from experts in the field.

Data abstraction

We assessed all studies for methodological quality in five specific areas: method of randomisation; clear allocation concealment; use of masked outcome assessments; use of an intention-to-treat analysis; and follow-up rates. Three reviewers independently assessed the articles for inclusion, and disagreements were resolved by discussion if unsolved after contacting authors.

We obtained information on disease characteristics and the training undertaken in the intervention groups. For participants who also self-adjusted therapy we extracted information on the actions triggered by self-measurements. We extracted descriptors on the population studied, including the number of participants who refused or were excluded from entering the trial. We sought information on the reasons for discontinuation of all participants allocated to the intervention.

Primary outcome measures were: thromboembolic events, major bleeding episodes, death from all causes, and proportion of measurements within the therapeutic range. Secondary outcomes included frequency of testing, minor bleeding episodes, and dropout rates.

Data analysis

We used Review Manager version 4.27 for the statistical analysis, and calculated odds ratios (ORs) and 95% CIs as summary statistics. We used a fixed-effects model with the Mantzel-Haenzel method to calculate the pooled OR, and used Peto's method to verify the results in uncommon outcomes. We examined heterogeneity in studies with the χ^2 and I^2 statistics.[19] Where significant heterogeneity existed we used the DerSimonian and Laird random-effects model.

We examined publication bias by constructing a funnel plot of precision (SE of the log OR) against ORs for the endpoints of major haemorrhage and thromboembolic episodes. In addition, we used Begg's rank correlation and Egger's linear regression tests to assess funnel plot asymmetry with STATA (Intercooled STATA B.2 for Windows).[20] A sensitivity analysis was done by excluding studies of the lowest quality and prespecified subgroup analyses according to clinical indication (mechanical valve replacement or atrial fibrillation), self-monitoring, and self-adjusted therapy. We did a post-hoc subgroup analysis according to provision of control group care (specialist anti-coagulation clinic care or family physician care). Meta-regression in STATA tested subgroup interaction on the outcomes.

The ratio of the average test frequency per individual patient per year between intervention and control was calculated, and linear regression was used to assess the association with study duration. Pooling of the mean percentage of tests in range was not possible; results were summarised with means and ranges.

A further substantial version of this review will appear in the Cochrane Library.

Role of the funding source

No funding source or sponsor had any role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 345 citations (figure 1). Of these, two authors screened 254 abstracts and identified potentially relevant studies (91 duplicate records were excluded). We independently reviewed 31 retrieved articles for inclusion criteria and data extraction. The reviewers were not masked to any aspect of the studies (eg, journal type, author names, or institution). A total of 14 articles met the eligibility criteria.

There were 14 randomised trials with a total of 3049 participants compared self-monitoring with routine anticoagulation (table 1).[21–34] Trials were from the UK (4),

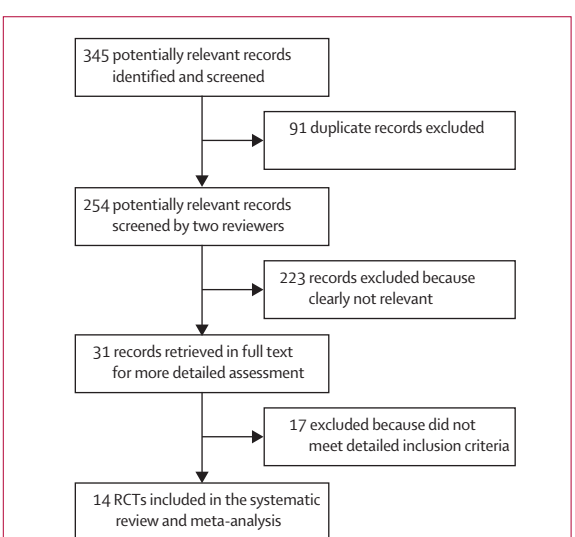

Figure 1: **Flowchart of search results**

	Inclusion criteria	Duration of study (months)	Mean age (years)	Numbers analysed		Control-group intervention	Education and intervention for self-monitoring group
				Control (n=1585)	Intervention (n=1464)		
White 1989, USA[34]	Inpatients receiving intravenous heparin with a planned duration of warfarin therapy of at least 8 weeks*	2	50	24	26	Specialist anticoagulation clinic care. Managed by nurse specialists	Patients managed directly by general internists
Horstkotte 1998, Germany[26]	Outpatients with isolated aortic or mitral valve replacement with the St Jude Medical prosthesis†	N/A	N/A	75	75	Managed by home physician	Standardised training, measured INR twice a week, and contacted coagulation clinic by phone
Sawicki 1999, Germany[30]	Any indication for anticoagulation and on life long treatment†	6	55	82	83	Twice-monthly adjustment by family doctor	Three educational sessions. Self adjusted
Beyth 2000, USA[21]	Inpatients aged >65 years receiving 10 000 units or more of intravenous heparin*	6	75	162	163	Managed by primary care physician as per usual practice	1-h education session, patients phoned results to coach who made recommendations
Cromheecke 2000, Netherlands[22]	Long-term anticoagulation, at least 6 months treatment†	3	42	49	49	Testing at intervals of 1-2 weeks and managed by a specialised anticoagulation service	Two educational sessions, self adjusted
Kortke 2001, Germany[28]	Permanent oral anticoagulation after mechanical heart valve surgery†	24	62·5	295	305	Managed by primary care physician as per usual practice	Trained in self-monitoring 6–11 days after operation
Sidhu 2001, UK[31]	Permanent oral anticoagulation after mechanical heart valve surgery performed by one surgeon†	24	61	48	34	Managed by family doctor as per usual practice	Two educational sessions, doctor availability to receive calls, patients self-adjusted as per protocol
Fitzmaurice 2002, UK[23]	Long-term anticoagulation at least 6 months treatment, with satisfactory INR control (INR within 0·5 of target value 60% of the time)†	6	63	26	23	Managed by primary care physician as per usual practice	Two educational workshops, daytime access to medical care. Self adjusted warfarin according to a dosing algorithm
Gadisseur 2003, Netherlands[24]	Long term oral anticoagulation at least 3 months treatment†	6	57	221	99	Routine care by anticoagulation clinic physicians	Three educational sessions. Self adjustment confirmed by telephone
Gardiner 2004, UK[25]	At least 8 months of oral anticoagulation treatment with a previous record of good compliance†	6	58	24	29	Testing every 4 weeks or more often if indicated by anticoagulation clinic staff	Two educational sessions 1 week apart
Khan 2004, UK[27]	At least 12 months treatment with warfarin patients with AF. Age >65 years†	6	Median 73	39	40	Managed by anticoagulation clinic, review according to INR	2-h education session, study co-ordinator liaised by phone and gave advice on dosage for next 7 days
Sunderji 2004, Canada[32]	Receiving warfarin for at least 1 month and required anticoagulation for at least 1 year‡	8	60	70	69	Managed by primary care physician as per usual practice	Two educational sessions, self adjusted using a nomogram
Menendez-Jandula 2005, Spain[29]	Any indication of anticoagulation and at least 3 months therapy†	11·8	66	369	368	Testing at least every 4 weeks and managed by a haematologist at an anticoagulation clinic	Two educational sessions, taught by nurse. Card system to aid self adjustment
Voller 2005, Germany[33]	Long-term oral anticoagulation in patients with non-valvular AF†	5	64	101	101	Managed by family doctor as per usual practice	Standard training course of three sessions

AF=atrial fibrillation. *Coumatrack monitor. †Coagucheck system. ‡Pro time microcoagulation system.

Table 1: **Study characteristics**

Germany (4), the Netherlands (2), the USA (2), Canada (1), and Spain (1). Three trials included only patients with life-long anticoagulation after insertion of a mechanical valve.[26,28,31] Two trials included patients on long-term anticoagulation for atrial fibrillation:[27,33] one of these[27] provided no reported outcomes in the control group. Nine trials included patients on long-term anticoagulation for any indication.[21–25,29,30,32,34] In seven trials the intervention groups adjusted therapy themselves;[22,23,29–33] five trials used non-adjusted therapy.[21,25–28] One further trial[24] reported information on adjusted (Gadisseur a) and non-adjusted therapy groups (Gadisseur b; table 1). Eight trials used primary care for the control group[21,23,26,28,30–33] and six studies used specialist anticoagulation clinics.[22,24,25,27,29,34] Duration of studies varied from 2 months to 24 months. Four trials were judged to be of poor quality[25,27,28,34] and removed in the sensitivity analysis. These four trials did not involve intention-to-treat analyses, were not masked, and crucially the allocation concealment was unclear.

No funnel plot asymmetry was noted for major haemorrhage (Begg's, p=0·86, Egger's, p=0·18) or thromboembolic events (Begg's, p=0·86, Egger's, p=0·50).

13 trials reported thromboembolic outcomes:[21–26,28–34] ten provided information to calculate the overall effect size. Self-monitoring more than halved thromboembolic events (figure 2). The findings were not affected by the removal of the four studies deemed to be of low quality (OR 0·41, 95% CI 0·25–0·70; p=0·001). In those trials where patients self-monitored and self-adjusted therapy,[22–24,29–33] the effect was larger than in those in which patients self-monitored only;[21,24,25,28,34] this subgroup interaction was not significant (p=0·12). In three trials

m	Mean INR within target range (%)		p	Time within range (%)		p
	Control group	Self-monitoring group		Control group	Self-monitoring group	
White 1989[34]	68	87	<0·001			
Horstkotte 1998[26]	22·3	43·2	<0·001			
Sawicki 1999[30]	43·2	53	0·22			
Beyth 2000[21]	-	-		32	56	<0·001
Cromheecke 2000[22]	49	55	0·06	-	-	
Kortke 2001[28]	60·5	78·3	<0·001			
Sidhu 2001[31]	58	67·60	<0·0001	63·8	76·5	<0·0001
Fitzmaurice 2002[23]	66 (61–71)*	72 (65–80)*	NS	77 (67–86)*	74 (67–81)*	NS
Gadisseur 2003[24]	61·3	65	0·14			
Gardiner 2004[25]	-	-		64 (26)	61 (20)	NS
Khan 2004[27]				70·4 (24·5) †	71·1 (14·5)†	NS
Sunderji 2004[32]	58·7 (5·8)†	64·8 (5·9)†	0·23	63·2 (5·8) †	71·8 (5·5)†	0·14
Menendez-Jandula 2005[29]	55·6 (19·6)†	58·6 (14·3)†	0·02	64·9 (19·9)	64·3 (14·3)	0·2
Voller 2005[33]	58·5 (19·8)†	67·8 (17·6)†	0·0061			

NS=non-significant (actual value not given). *95 % CIs. †SDs.

Table 2: **Mean INR within target range**

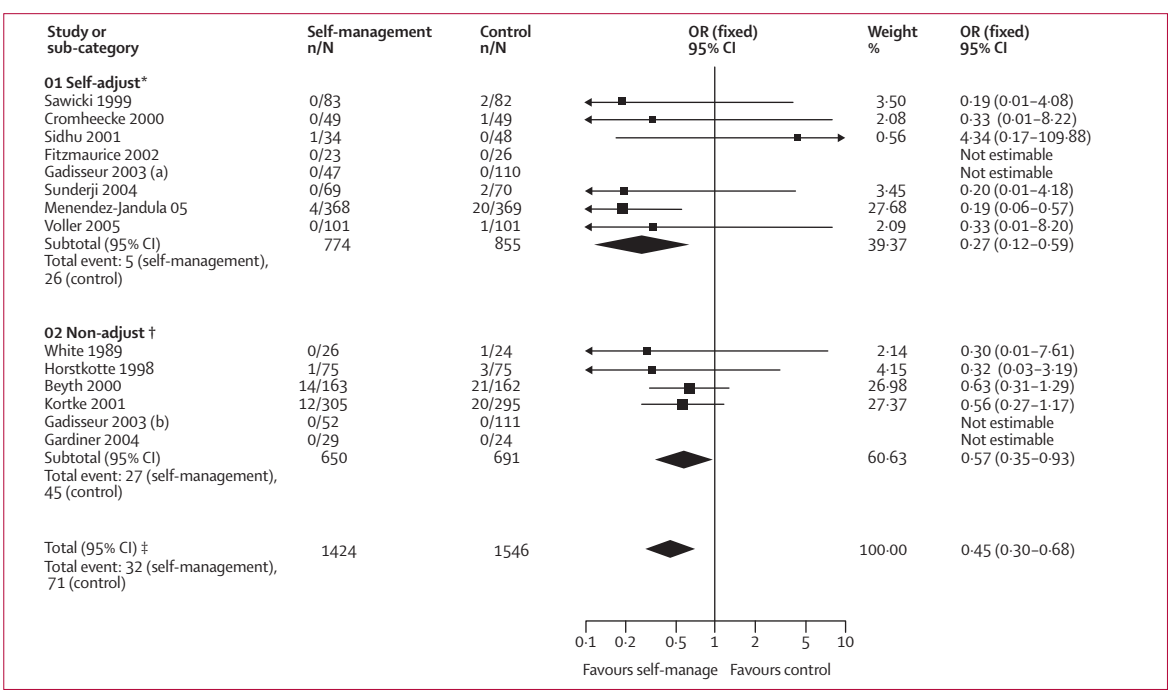

Figure 2: **Self-monitoring and thromboembolic events from fixed-effects model**

in which patients had mechanical valves[26,28,31] there was a non-significant effect on thromboembolic events (0·60, 0·31–1·17; p=0·13). The post-hoc subgroup analysis suggested a greater reduction when compared with specialised care OR (0·21, 0·08–0·55; p=0·002) than when compared with family physician care OR (0·56, 0·35–0·90; p=0·02).

12 trials reported major haemorrhage outcomes:[21–25,28–34] ten provided information to calculate the overall effect size. Self-monitoring was associated with a significant one-third reduction in major haemorrhage (figure 3). Excluding the four studies deemed to be of low quality increased the uncertainty of the effect (0·66, 0·37–1·16; p=0·15). In the studies with patients who self-monitored only,[21,24,25,28,34] there was a significant reduction in events. There was a non-significant effect in those studies with patients who self-monitored and self-adjusted therapy;[22–24,29–33] but the subgroup interaction was not significant (p=0·32). A post-hoc subgroup analysis implied a greater reduction in family physician OR (0·61, 0·38–0·99; p=0·05) than in specialised care OR (0·82, 0·31–2·17; p=0·68).

Ten trials reported information on death:[21,23,25,27,29–34] six provided information to calculate the overall effect size. Self-monitoring was associated with a significant reduction in death from all causes (figure 4). The

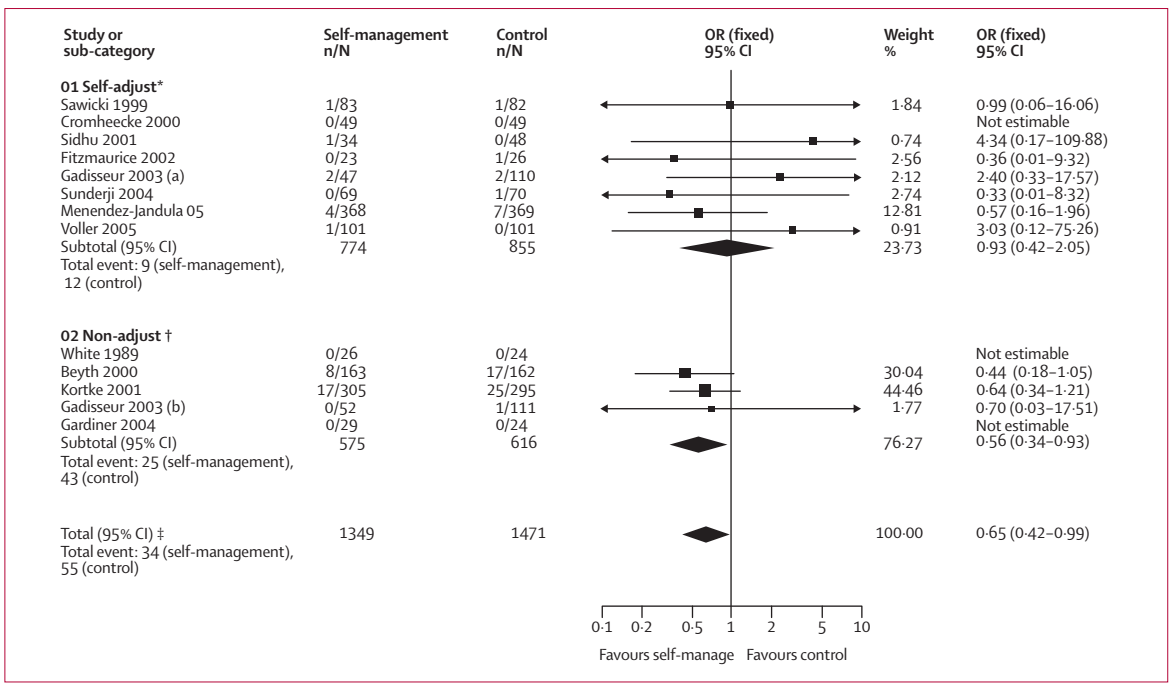

Figure 3: **Self-monitoring of major haemorrhage from fixed-effects model**

findings were not affected by the removal of the four studies deemed to be of low quality (0·58, 0·36–0·95; p=0·03). A significant reduction in death was noted in self-monitoring and self-adjusted therapy.[23,29–33] A non-significant effect was recorded in the self-monitoring only trials;[21,25,27,34] subgroup interaction was not significant (p=0·17). Insufficient information was provided to pool results by clinical condition. The post-hoc subgroup analysis suggested a greater reduction in specialised care OR (0·47, 0·19–1·13; p=0·09) than in family physician care OR (0·61, 0·38–0·98; p=0·04).

11 trials reported mean INR results within target range (table 2).[22–24,26,28–34] All 11 studies reported improvements in the self-monitoring groups, and six were significant.[26,28,29,31,33,34] Pooling of the mean proportion of tests in range was not possible because information was obtained in two different ways: either the proportion of overall tests in range,[22,23,26,28,30–34] or the proportion of tests of each individual in range.[24,29] Improvements ranged from 3·0% to 20·9%. Seven trials reported the proportion of time within range.[21,23,25,27,29,31, 32] Of these, four reported an improvement in the self-monitoring group, and two were significant.[21,32] Three trials reported a non-significant improvement in the control group.[23,25,29]

Nine trials (1575 participants) reported outcomes on minor haemorrhage.[23,24,26,29–34] Heterogeneity in these trials prevented pooling (p=0·01 for heterogeneity, I^2=64%). One trial[29] showed a significant effect on minor haemorrhage in terms of self-monitoring (OR 0·31, 0·22–0·44). Three reported a non-significant increase in minor haemorrhage in the intervention group.[23,30,31]

Nine studies reported the total number of tests done throughout the study (table 3).[23,24,26,28,29,31–34] Seven trials used family physician management in the control group. The maximum test frequency was in the study with the shortest duration.[34] The ratio of tests in the self-

	Duration of study (months)	Total number of tests		Number of tests per person per year		Ratio of tests
		Control group	Self-monitoring group	Control group	Self-monitoring group	Control/ self-monitoring
White 1989[34]	2	190	427	47·50	98·54	2·07
Voller 2005[33]	5	793	2072	18·84	49·24	2·61
Gadisseur 2003[24]	6	2068	2530	18·71	51·11	2·73
Fitzmaurice 2002[23]	6	138	336	10·62	29·22	2·75
Sunderji 2004[32]	8	1157	1923	24·79	41·80	1·69
Menendez-Jandula 2005[29]	11·8	4712	15 435	12·99	42·65	3·28
Horstkotte 1998[26]	18	2166	9982	19·31	93·58	4·85
Sidhu 2001[31]	24	1060	3136	11·04	46·12	4·18
Kortke 2001[28]	24	4599	23 693	7·79	38·84	4·98

Table 3: **Test frequency**

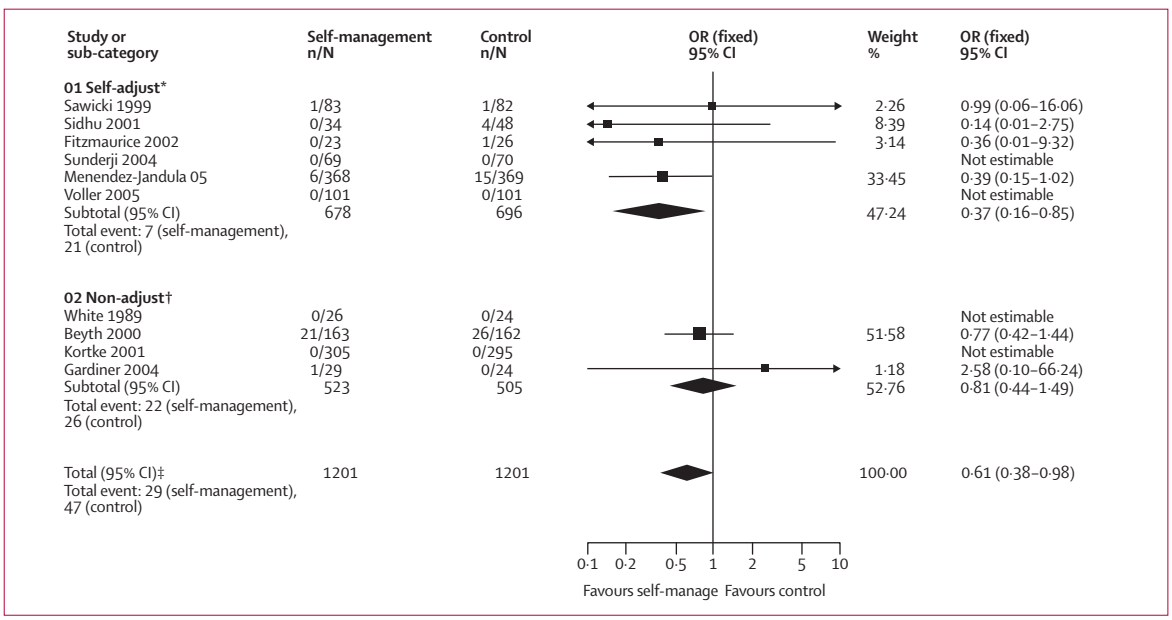

Figure 4: **Self-monitoring and death from fixed-effects model**

monitoring group compared with the control groups ranged from 1·69 to 4·98: this increased with duration of study (test for linear trend p=0·0015).

A population of 7579 was sampled in eight trials.[21,23,24–27,29–30] Of these, 5527 were either excluded or decided not to take part. On average, the proportion of people who could not (or would not) take part was 62%, with a range from 31% to 88%. The exclusion rates were much higher in trials that included older populations (mean age 75 years).[21] Of the patients assigned to the intervention, 22% (range 9–43%) were unable to complete self-monitoring. The main reasons for the dropouts were: problems with the monitoring device, physical limitations preventing self-monitoring, problems attending training, or failing the training assessment.

Discussion

Although no trial alone was significant, the combined trials suggest that self-monitoring of oral anticoagulation leads to a significant one-third reduction in death from all causes. Both benefits and harms of anticoagulation seem to be improved by self-monitoring: thromboembolism was decreased by 55%, and major haemorrhage was also decreased. In those who also self-adjusted therapy, there seemed to be a greater reduction in thromboembolic events and mortality than self-monitoring alone, but at a cost of less reduction in haemorrhage.

This systematic review adds to three previous reviews of self-monitoring of oral anticoagulation. One previous review,[35] which included eight trials, identified a significant reduction in major clinical events (OR 0·62, 95% CI 0·43–0·90; p<0·01), and another review[36] of four randomised trials concluded that self-management by patients is safe and can improve the quality of anticoagulation control. A review identifying 12 trials (seven randomised controlled trials and five quasi-experimental trials)[37] concluded that patients undertaking self-management remained in the therapeutic range for the same time or longer than patients under usual care, and that the incidence of adverse effects was the same or less than patients under usual care.

Our review has some potential limitations. First, though our search was comprehensive, the potential exists for missing both published and unpublished studies. 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 monitoring of anticoagulation. Specialist programmes might improve outcomes by the same mechanism as self-monitoring, 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 readings than those allocated to routine care.[24,27] Third, in some trials the outcome measures were not assessed masked, and intention-to-treat analysis was not used in all trials, which could have inflated the apparent results.[38,39] Fourth, it was not possible to combine the proportion of tests in range, nor the mean time in range, nor determine the rate of outlier values. To further understand the effect of self-monitoring on both the time in range and tests in range, an individual patient data meta-analysis is needed. Finally, the longest trial was only 2 years in duration, although long-term benefits have been seen for self-management in a non-randomised study over 5 years.[40]

Intrinsic limitations to self-monitoring include the reluctance of individuals to participate and the extensive training required. An additional problem of this method in clinical practice is the high cost of the test strips. The reliability of self-monitoring devices can affect test results; however available devices give INR results that are similar to those obtained in laboratory testing.[41] Self-monitoring is also associated with a rate of testing that is higher than that of usual care. In effect, self-adjusted dosing with warfarin is analogous to self-adjusted dosing with insulin according to a prespecified sliding scale.[42] Such self-adjusted treatment has been practised for years by diabetics.[42] Self-monitoring offers independence and freedom of travel to selected patients.

Self-monitoring can improve the quality of oral anticoagulation therapy, with patients more frequently in the therapeutic range, while improving benefits and decreasing harms. However, self-monitoring is not feasible for all patients, and requires identification and education of suitable candidates. Guidelines exist for institutions considering implementation of self-monitoring of anticoagulation.[41]

Contributors

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. J M Garcia-Alamino organised the study concept and design. C Heneghan, E Meats, J M Garcia-Alamino, and P Alonso-Coello acquired the data. C Heneghan, J M Garcia-Alamino, R Perera, P Alonso-Coello, and P Glasziou analysed and interpreted data. C Heneghan, R Perera, J M Garcia-Alamino, P Alonso-Coello, and P Glasziou drafted the manuscript. Statistical analysis was done by R Perera, C Heneghan, and P Glasziou.

Conflict of interest statement

We declare that we have no conflict of interest.

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References

1 The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation. *N Engl J Med* 1990; **323:** 1505–11.

2 EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993; **342:** 1255–62.

3 Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996; **348:** 633–38.

4 Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. *J Am Coll Cardiol* 1991; **18:** 349–55.

5 Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with non-rheumatic atrial fibrillation. *N Engl J Med* 1992; **327:** 1406–12.

6 Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation. How well do randomized trials translate into clinical practice? *JAMA* 2003; **290:** 2685–92.

7 Buckingham TA, Hatala R. Anticoagulants for atrial fibrillation: why is the treatment rate so low? *Clin Cardiol* 2002; **25:** 447–54.

8 Hylek EM, Skates SJ, Sheehan MA, et al. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with non-rheumatic atrial fibrillation. *N Engl J Med* 1996; **335:** 540–46.

9 Cannegieter SC, Rosendaal FR, Wintzen AR, et al. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 1995; **333:** 11–17.

10 Kearon C, Ginsberg J, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; **349:** 631–39.

11 Gottlieb LK, Salem-Chatz S. Anticoagulation in atrial fibrillation: does efficacy in clinical trials translate into effectiveness in practice? *Arch Intern Med* 1994; **154:** 1945–53.

12 Bernardo A, Halhuber C, Horstkotte D. Home prothrombin estimation. In: Butchart EG, Bodnar E, eds. Thrombosis, embolism, and bleeding. London: ICR Publishers, 1992: 325–30.

13 Douketis JD. Patient self-monitoring of oral anticoagulant therapy. Potential benefits and implications for clinical practice. *Am J Cardiovasc Drugs* 2001;1: 245–51.

14 Ansell JE. Empowering patients to monitor and manage oral anticoagulation therapy . *JAMA* 1999; **281:** 182–83.

15 Hobbs F. Near patient testing in primary care. *BMJ* 1996; **312:** 577–80.

16 Taborski U, Muller-Berghaus G. State-of-the-art patient self-management for control of oral anticoagulation. *Semin Thromb Hemost* 1999; **25:** 43–47.

17 Fitzmaurice DA, Machin SJ. Recommendations for patients undertaking self-management of oral anticoagulation. *BMJ* 2001; **323:** 985–89.

18 Dickersin K, Manheimer E, Wieland S, Robinson KA, Lefebvre C, McDonald S. Development of the Cochrane Collaboration's CENTRAL Register of controlled clinical trials. *Eval Health Prof* 2002; **25:** 38–64.

19 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557–60.

20 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315:** 629–34.

21 Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin: a randomized, controlled trial. *Ann Intern Med* 2000; **133:** 687–95.

22 Cromheecke ME, Levi M, Colly LP, et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. *Lancet* 2000; **356:** 97–102.

23 Fitzmaurice DA, Murray ET, Gee KM, Allan TF, Hobbs FD. A randomised controlled trial of patient self management of oral anticoagulation treatment compared with primary care management. *J Clin Pathol* 2002; **55:** 845–49

24 Gadisseur AP, Breukink-Engbers WG, van der Meer FJ, van den Besselaar AM, Sturk A, Rosendaal FR. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in the Netherlands: a randomized clinical trial. *Arch Intern Med* 2003; **163:** 2639–46.

25 Gardiner C, Williams K, Mackie IJ, Machin SJ, Cohen H. Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring. *Br J Haematol* 2005; **128:** 242–47.

26 Horstkotte D, Piper C, Wiemer M. Optimal frequency of patient monitoring and intensity of oral anticoagulation therapy in valvular heart disease. *J Thromb Thrombolysis* 1998; **5** (suppl 1)**:** 19–24.

27 Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. *Br J Haematol* 2004; **126:** 557–64.

28 Kortke H, Korfer R. International normalized ratio self-management after mechanical heart valve replacement: is an early start advantageous? *Ann Thorac Surg* 2001; **72:** 44–48.

29 Menendez-Jandula B, Souto JC, Oliver A, et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. *Ann Intern Med* 2005; **142:** 1–10.

30 Sawicki PT. A structured teaching and self-management program for patients receiving oral anticoagulation: a randomized controlled trial. *JAMA* 1999; **281:** 145–50.

31 Sidhu P, O'Kane HO. Self-managed anticoagulation: results from a two-year prospective randomized trial with heart valve patients. *Ann Thorac Surg* 2001; **72:** 1523–27.

32 Sunderji R, Gin K, Shalansky K, et al. A randomized trial of patient self-managed versus physician-managed oral anticoagulation. *Can J Cardiol* 2004; **20:** 1117–23.

33 Voller H, Dovifat C, Glatz J. Home management of anticoagulation. *Eur Heart J Suppl* 2001; **3** (suppl Q)**:** Q44–49.

34 White RH, McCurdy SA, von Marensdorff H, Woodruff DE Jr, Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy: a randomized, prospective study. *Ann Intern Med* 1989; **111:** 730–37.

35 Odegaard KJ. [Self-management in anticoagulation—a meta-analysis] *Tidsskr Nor Laegeforen* 2004; **124:** 2900–03.

36 Siebenhofer A, Berghold A, Sawicki PT. Systematic review of studies of self-management of oral anticoagulation. *Thromb Haemost* 2004; **91:** 225–32.

37 de Sola-Morales Serra O, Elorza Ricart JM. Portable coagulometers: a systematic review of the evidence on self-management of oral anticoagulant treatment. *Med Clin (Barc)* 2005; **124:** 321–25.

38 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17:** 1–12.

39 Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999; **319:** 670–74.

40 Sawicki PT, Glaser B, Kleespies C, et al. Self-management of oral anticoagulation: long-term results. *J Intern Med* 2003; **254:** 515–16.

41 Ansell J, Jacobson A, Levy J, Voller H, Hasenkam JM. Guidelines for implementation of patient self-testing and patient self-management of oral anticoagulation. International consensus guidelines prepared by International Self-Monitoring Association for Oral Anticoagulation. *Int J Cardiol* 2005; **99:** 37–45.

42 Ansell JE, Hughes R. Evolving models of warfarin management: anticoagulation clinics, patient self-monitoring, and patient self-management. *Am Heart J* 1996; **132:** 1095–100.