Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data

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Lancet 2012; 379: 322–34

Published Online December 1, 2011 DOI:10.1016/S0140-6736(11)61294-4

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Summary

Background **Uptake of self-testing and self-management of oral coagulation has remained inconsistent, despite good evidence of their effectiveness. To clarify the value of self-monitoring of oral anticoagulation, we did a meta-analysis of individual patient data addressing several important gaps in the evidence, including an estimate of the effect on time to death, first major haemorrhage, and thromboembolism.**

Methods **We searched Ovid versions of Embase (1980–2009) and Medline (1966–2009), limiting searches to randomised trials with a maximally sensitive strategy. We approached all authors of included trials and requested individual patient data: primary outcomes were time to death, first major haemorrhage, and first thromboembolic event. We did prespecified subgroup analyses according to age, type of control-group care (anticoagulation-clinic care *vs* primary care), self-testing alone versus self-management, and sex. We analysed patients with mechanical heart valves or atrial fibrillation separately. We used a random-effect model method to calculate pooled hazard ratios and did tests for interaction and heterogeneity, and calculated a time-specific number needed to treat.**

Findings **Of 1357 abstracts, we included 11 trials with data for 6417 participants and 12 800 person-years of follow-up. We reported a significant reduction in thromboembolic events in the self-monitoring group (hazard ratio 0·51; 95% CI 0·31–0·85) but not for major haemorrhagic events (0·88, 0·74–1·06) or death (0·82, 0·62–1·09). Participants younger than 55 years showed a striking reduction in thrombotic events (hazard ratio 0·33, 95% CI 0·17–0·66), as did participants with mechanical heart valve (0·52, 0·35–0·77). Analysis of major outcomes in the very elderly (age ≥85 years, n=99) showed no significant adverse effects of the intervention for all outcomes.**

Interpretation **Our analysis showed that self-monitoring and self-management of oral coagulation is a safe option for suitable patients of all ages. Patients should also be offered the option to self-manage their disease with suitable health-care support as back-up.**

Funding **UK National Institute for Health Research (NIHR) Technology Assessment Programme, UK NIHR National School for Primary Care Research.**

Introduction

Oral anticoagulation with vitamin K antagonists substantially reduces the incidence of thromboembolic events.[1–4] Although the number of patients receiving oral anticoagulants has consistently increased, uptake is limited by requirements to maintain the international normalised ratio (INR) within a narrow target range, which includes frequent testing and appropriate dose adjustments. Benefits shown in clinical trials might not translate into routine practice: namely the risk of major bleeding could be high in specific populations of patients, especially in the elderly.[2]

Introduction of reliable and analytically accurate point-of-care devices allows self-testing by the patient in the home setting.[1,2] Patients can have their test result managed by their health-care provider (self-testing) or they can interpret their INR result, and adjust their own dose of anticoagulant accordingly (self-management).

Previous systematic reviews[4–6] showed that self-monitoring is a safe intervention, which gives rise to significant reduction in thromboembolic events, while reducing the risk of death. Additionally, patients spend more time in the therapeutic range of INR than they would without self-monitoring. However, previous conclusions were limited by methodological problems and inadequate reporting of important outcome data over time.[4–6] Also important subgroup analyses, stratified by age and indication for anticoagulation therapy, have not been possible.

Uptake of self-testing and self-management has remained inconsistent in and between countries, despite good evidence of their effectiveness and guidelines encouraging patients to discuss this option with clinical staff.[1,7,8] To clarify further the value of self-monitoring of oral anticoagulation we did a meta-analysis of individual patient data, which updated our previous systematic reviews and enabled more detailed analysis than previously. Specifically, we aimed to address several important gaps in the evidence, including obtaining an estimate of the effect of self-monitoring on time to death, first major haemorrhage, and first thromboembolic event. We also aimed to investigate effects in important subgroups such as the elderly and those with specific disease indications for anticoagulation such as atrial fibrillation or mechanical heart valve.

Methods

Search strategy and study selection

The protocol methods have been previously published.[9] We used the same search strategy as for previous reviews.[4–6] We searched Ovid versions of Embase (1980–2009) and Medline (1966–2009), limiting searches to randomised trials with a maximally sensitive strategy.[10] A list of search terms is shown in webappendix pp 1–3. We modified these searches for the Cochrane Central Register of Controlled Trials, the Cochrane Library, issue 2, 2009, and Cinahl (1982–2009). We also searched for trials that are still underway or unpublished (eg, UK National Research Register and Trials Central), and handsearched reference lists of retrieved papers.

Trial eligibility and quality assessment

We included randomised trials that 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 on anticoagulant therapy irrespective of the indication for treatment, with no language restrictions.

As in our previous systematic review,[5] we assessed the quality of studies by the presence of randomisation, allocation concealment, masked outcome assessments, intention-to-treat analysis, and attrition rates. Two reviewers (CH and AW) independently assessed the articles for inclusion, and disagreements were resolved by discussion.

Data extraction

We approached all authors whose trials met the inclusion criteria and requested the following data for individual patients: date of randomisation, age, indication for treatment, type of care, demographic and psychosocial characteristics at randomisation including quality-of-life measures, treatment allocation, time to death, time to first major haemorrhage, time to first thromboembolic event, and INR measurements.

Data validation

We kept original data on a secure server with a back-up copy according to a prespecified data-security-agreement policy. Two researchers (CB and AF) cross-checked trial details, summary measures, and major outcomes were cross-checked with prespecified outcome definitions against published articles. Any inconsistencies were discussed with the original trialist and corrections were made when appropriate. Requirements for authorship were those of the International Committee of Medical Journal Editors and a representative of each trial was invited to an investigators' meeting before publication to discuss analysis and results.

Statistical analysis

Primary outcomes were time to death, first major haemorrhage, and first thromboembolic events. Major haemorrhages included: 1) bleeding that was fatal, 2) symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; and 3) bleeding causing a fall in haemoglobin concentrations of 20 g/L (1·24 mmol/L) or more, or leading to transfusion of two units of packed red-blood cells. Thromboembolic events were stroke, arterial embolism, symptomatic deep-vein thrombosis, or pulmonary embolism.[11]

See Online for webappendix

One secondary outcome was time in therapeutic range. For individual data, time-to-event outcomes were summarised as log (hazard ratio), and time in range as mean (SD). We used the survival-curve and hazard-ratio programme SCHARP (version 4) for meta-analysis of individual patient data. SCHARP is an SAS application for meta-analysis of individual patient data with a point-and-click interface that produces publication-quality graphs and appropriate summary statistics for time-to-event data.[12]

We used SPSS (version 17) for analysis of baseline characteristics. We did prespecified subgroup analyses for the primary outcomes with the following age bands (<55, 55–64, 65–74, and ≥75 years), the type of control-group care, type of self-monitoring, and sex. We also analysed patients who had mechanical heart valves, atrial fibrillation, and other indications separately, stratifying them by age (<65 years and ≥65 years).

Because the components of the interventions differ somewhat (eg, in terms of their training and education) and in assuming a different underlying effect for each trial intervention, a random effects model was used to calculate pooled hazard ratios. Random effects generally lead to wider CIs than the fixed effects; however, when no heterogeneity is present the results of the fixed and random effects are equivalent. Time-to-event outcomes were analysed with hazard ratios, which take into account the number and timing of events, and the time until last follow-up for each patient not experiencing an event. We used a two-step process for meta-analysis: a hazard ratio was estimated for each trial and then hazard ratios were pooled in a meta-analysis. The log-rank observed-minus-expected statistic and its variance were calculated for each trial.[13] We examined heterogeneity with the I^2 statistics.[14,15] We also did tests for interaction between subgroups of patients, partitioning the total heterogeneity across all trials into within-group and between-group heterogeneity (the test for interaction). We calculated a time-specific number needed to treat at various timepoints with the method outlined by Altman and Andersen,[16]

$$\text{Number needed to treat} = \frac{1}{(\text{Sc}[t]^h - \text{Sc}[t])}$$

where at a specified timepoint (t), the survival probability in the control group is Sc(t), then the survival probability in the active group is $Sc(t)^h$, where h is the hazard ratio comparing the treatment groups. The number needed to treat represents the number of patients treated in the intervention group for one less primary outcome event over the time stipulated. For subgroups, we calculated the average effect over 5 years based on the control event rate. All analyses were on an intention to treat basis. We deviated from our original protocol in that we did not present data on psychological factors, which we hope to report elsewhere.

Sufficient data from eight trials[17–24] were available for us to calculate the mean time in therapeutic range at timepoints of 7 days, 30 days, 90 days, 6 months, and 1 year by the method of linear interpolation set out by Rosendaal and colleagues.[25] We assessed publication bias by constructing a funnel plot of precision (SE of the log hazard ratio) against hazard ratio for the endpoints of major haemorrhage and thromboembolic events,[6] and did Begg's and Egger's tests.[15]

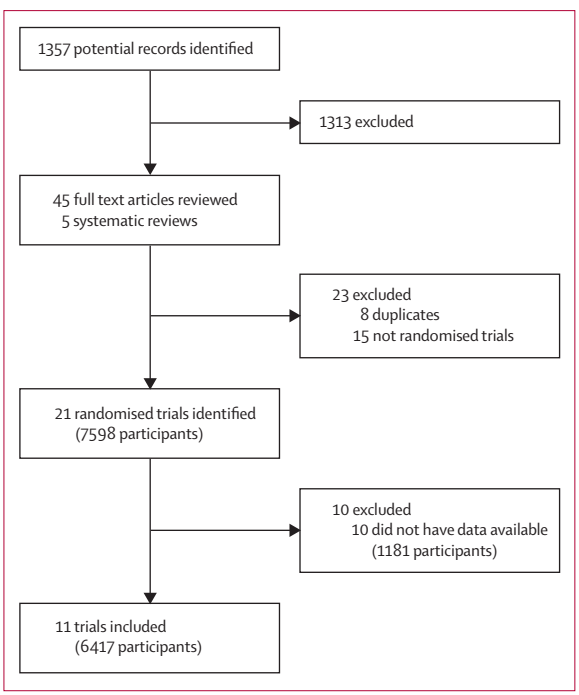

Figure 1: **Flow chart of studies**

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or 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

Of 1357 abstracts, we identified 21 trials (20 published, one unpublished) that met the eligibility criteria (figure 1). We were unable to obtain adequate data from

	Country	Dates of recruitment	Year of publication of primary results	Study duration (months)	Age range, years (mean)	Total number of patients	Female	Atrial fibrillation	Mechanical valve	Other	Self management	Type of control group care
Beyth et al[36]*	USA	1992–95	2000	6	65–94 (74·7)	325 (5%)	184 (57%)	54 (17%)	36 (11%)	235 (72%)	No	Primary Care
Cromheecke et al[17]†	Holland	1998	2000	3	22–71 (42·3)	49 (1%)	21 (43%)	11 (22%)	23 (47%)	15 (31%)	Yes	Anticoagulation clinic
Koertke et al[18]†	Germany	1994–97	2001	24	17–77 (59·7)	930 (14%)	293 (32%)	..	930 (100%)	..	Yes	Primary care
Sunderji et al[37]‡	Canada	1998–2002	2004	20	20–85 (60·0)	139 (2%)	41 (29%)	47 (34%)	82 (59%)	10 (7%)	Yes	Primary care
Menéndez-Jándula et al[19]†	Spain	2001–02	2005	12	19–90 (63·5)	737 (11%)	347 (47%)	296 (40%)	285 (39%)	154 (21%)§	Yes	Anticoagulation clinic
Völler et al[38]†	Germany	1999–2001	2005	19¶	36–85 (64·4)	202 (3%)	53 (26%)	202 (100%)	..	..	Yes	Primary care
Fitzmaurice et al[20]†	UK	2001–02	2005	12	18–87 (65·1)	617 (10%)	217 (35%)	343 (56%)	97 (16%)	177 (29%)	Yes	Both
Christensen et al[21]†	Denmark	2002–03	2006	6	21–78 (50·7)	100 (2%)	33 (33%)	24 (24%)	35 (35%)	41 (41%)	Yes	Both
Siebenhofer et al[23]†	Austria	2002–05	2007	36	60–89 (68·8)	195 (3%)	81 (42%)	89 (46%)	32 (16%)	74 (38%)	Yes	Both
Matchar et al[22]‡	USA	2003–06	2010	36	23–90 (67·0)	2922 (46%)	51 (2%)	2236 (77%)||	684 (23%)	2 (<1%)	No	Anticoagulation clinic
Kaatz et al[24]†	USA	1998–99	2001	12	30–87 (64·1)	201 (3%)	84 (42%)	86 (43%)	39 (19%)	76 (38%)	No	Anticoagulation clinic
Totals	..	1992–2006	2000–10	..	17–94 (65·0)	6417	1405 (22%)	3388 (53%)	2243 (35·0%)	784 (12%)	..	..

Data are range (mean) or number (%). *Coumatrack monitor.†Coaguchek system. ‡Pro time microcoagulation system.§Two patients were unclassified for indication. ¶Study stopped early. ||2236 with no mechanical heart valve, 2422 had atrial fibrillation, mechanical heart valve, or both.

Table 1: **Characteristics of studies**

ten trials.[26–35] These trials were small, ranging from 50–320 participants (total 1181 participants). Of 21 original trials, including 7598 participants, we present results for 6417 (84%) participants.

Table 1 shows 11 included trials: three in the USA,[22,24,36] two in Germany,[18,38] and one each from Austria and Germany,[23] Canada,[37] Denmark,[21] Netherlands,[17] Spain[19] and the UK.[20] Participant recruitment into the trials occurred from 1992 to 2006, and trials were published between 2000 and 2010. The Coaguchek (Roche Diagnostics, Basel, Switzerland), Pro time micro-coagulation (ITC Nexus Dx, Edison, NJ USA), and the Coumatrak monitor (Du Pont Pharmaceuticals, Wilmington, DE, USA) systems were used (table 1). For all trials, we verified clear methods for randomisation, allocation concealment, and intention-to-treat analyses. For publication bias, we saw no funnel-plot asymmetry and no bias with Begg's test: p=0·35 for thromboembolic events and p=1·00 for major haemorrhage; corresponding results of Egger's test were p=0·05 for thromboembolic events and p=0·92 for major haemorrhage. 3266 (51%) participants were randomly allocated to self-monitoring and 3151 to conventional care. Participants in the intervention group were on average 1·7 years (64·2 [SD 11·7] years *vs* 65·9 [SD 10·5] years; p<0·0001) younger than those in the control groups. A wide range of ages was included: from 17 to 94 years of age, with 99 participants aged 85 years or older. 12 800 person years of follow-up were obtained (mean 1·99 years [SD 1·22]), with a maximum follow-up of 1888 days (5·17 years).

Over a third of participants had a mechanical heart valve insertion; one trial[18] included only participants with this indication. Over half of participants had atrial fibrillation; one trial[38] included only participants with this indication. For other disorders, over 10% of participants from nine trials[17,19–24,36,37] were included. In eight trials,[17–21,23,37,38] just under half (46%) of those in the intervention group used self-management and in three trials,[22,24,36] just over half (54%) used self-testing only with dose adjustments undertaken by their regular clinician (table 1).

In four trials[18,36–38] including a quarter of participants, primary care was used as the control and in another four trials[17,19,22,24] including more than half (61%) of participants, specialist anticoagulation clinics were used (table 1). In the three remaining trials,[20,21,23] the control included either primary care or specialist clinics (table 1).

A significant reduction in thromboembolic events was seen in the self-monitoring group (hazard ratio 0·51, 95% CI 0·31–0·85; p=0·010; I^2=52·6%; figure 2). At 1 year, the number needed to treat to prevent one thromboembolic event was 78 (95% CI 55–253), and by 5 years it was 27 (19–87; table 2). Individual study hazard ratios are shown in webappendix p 4. No significant reduction in major haemorrhagic events (hazard ratio 0·88, 95% CI, 0·74–1·06; p=0·18, I^2=0) or in deaths

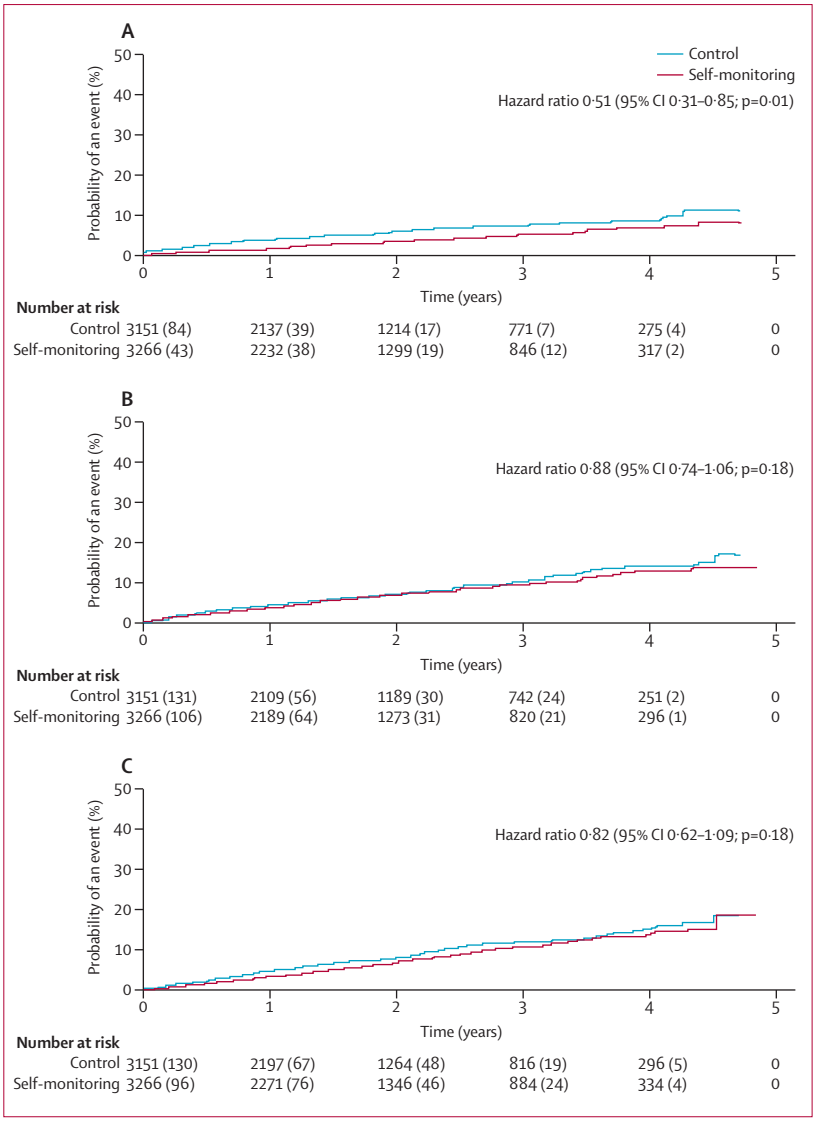

Figure 2: **Hazard ratios for major outcomes**
Hazard ratios for thrombotic events (152 events in the control group, 114 in the self-monitoring group; A), haemorrhagic events (244 in the control group, 230 in the self-monitoring group; B), and death (274 in the control group, 247 in the self-monitoring group; C).

(0·82, 0·62–1·09; p=0·18; I^2= 37·0) were apparent with self-monitoring (figure 2).

In prespecified subgroups the rate of thromboembolic events in men was significantly reduced in the self-monitoring group (figure 3; p=0·010; I^2=61·3) whereas in women it was not (figure 3; p=0·46; I^2=26·6;). However, the ratio of male to female participants was four to one (5012 men *vs* 1405 women) and the interaction test showed that these two subgroups did not differ significantly (χ^2 0·01; p=0·94). Participants younger than 55 years of age who self-monitored had a striking reduction in thromboembolic events (figure 3; p=0·002; I^2=0), whereas in other age groups non-significant effects were shown. In participants younger than 55 years, this

	Number needed to treat (95% CI)	Number of patients still at risk
All participants (N=6417)		
Thrombosis		
Year 1	78 (55 to 253)	4369
Year 2	47 (33 to 154)	2513
Year 3	36 (26 to 119)	1617
Year 4	32 (23 to 104)	592
Year 5	27 (19 to 87)	..
Major Haemorrhage		
Year 1	205 (94 to ∞)	4598
Year 2	123 (59 to ∞)	2462
Year 3	96 (44 to ∞)	1564
Year 4	74 (34 to ∞)	547
Year 5	70 (32 to ∞)	..
Death		
Year 1	137 (65 to ∞)	4468
Year 2	82 (39 to ∞)	2610
Year 3	55 (26 to ∞)	1700
Year 4	47 (22 to ∞)	630
Year 5	42 (20 to ∞)	..
Mechanical valve only (n=2243)		
Thrombosis		
Year 1	55 (41 to 116)	1721
Year 2	37 (28 to 78)	589
Year 3	33 (25 to 70)	419
Year 4	31 (23 to 65)	186
Year 5	24 (18 to 50)	0
Major haemorrhage		
Year 1	127 (66 to ∞)	1699
Year 2	65 (34 to ∞)	565
Year 3	43 (22 to ∞)	386
Year 4	31 (16 to ∞)	160
Year 5	29 (15 to ∞)	..
Death		
Year 1	156 (67 to ∞)	1763
Year 2	65 (34 to ∞)	618
Year 3	43 (23 to ∞)	442
Year 4	31 (16 to ∞)	202
Year 5	29 (15 to ∞)	..
Atrial fibrillation only (n=3388)		
Thrombosis		
Year 1	185 (85 to ∞)	2386
Year 2	91 (42 to ∞)	1860
Year 3	65 (30 to ∞)	1163
Year 4	54 (25 to ∞)	393
Year 5	49 (23 to ∞)	..
Major haemorrhage		
Year 1	675 (79 to ∞)*	2344
Year 2	453 (53 to ∞)*	1824
Year 3	342 (40 to ∞)*	1134
Year 4	268 (32 to ∞)*	373
Year 5	255 (30 to ∞)*	..

(Continues in next column)

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	Number needed to treat (95% CI)	Number of patients still at risk
Death		
Year 1	101 (50 to ∞)	2428
Year 2	56 (28 to ∞)	1921
Year 3	37 (18 to ∞)	1216
Year 4	30 (15 to ∞)	413
Year 5	26 (13 to ∞)	..

The number needed to treat is estimated as:

$$\text{Number needed to treat} = \frac{1}{(Sc[t]^h - Sc[t])}$$

*Number needed to harm.

Table 2: **Number needed to treat at various timepoints for all self-monitoring participants with a mechanical valve and atrial fibrillation compared with standard care**

result corresponded to a number needed to treat of 21 (95% CI 17–42) to prevent one thromboembolic event at 1 year. Non-significant improvement in major outcomes was seen in the self-monitoring group with younger age (χ^2 7·75; p=0·052).

In terms of indication, participants with a mechanical heart valve who self-monitored had significant reductions in thromboembolic events (figure 3; p=0·001; I^2=0). At 1 year the number needed to treat to prevent one event was 55 (95% CI 41–116) and by 5 years it was 24 (18–50). Effects for both atrial fibrillation (figure 3; p=0·35; I^2=40·9) and other indications (figure 3; p=0·12; I^2=0) were not significant. An interaction test (χ^2 6·88, p=0·032) between indications was significant. Participants who self-managed oral anticoagulation also had significantly fewer thromboembolic events (figure 4; p<0·001; I^2=0), whereas participants self-testing alone did not (figure 4; p=0·51; I^2=50·3). The interaction test between self-testing and self-management for this difference was significant (χ^2 9·81, p=0·002). For participants self-managing, the number needed to treat to prevent one thromboembolic event was 39 (95% CI 31–65). For major haemorrhage and death, we detected no significant effects or interactions by age, sex, indication, or type of monitoring (figure 3).

Analysis of major outcomes in the very elderly (≥85 years, n=99) showed no significant adverse effects of self-monitoring for all outcomes, and a reduction in mortality was seen (hazard ratio 0·44, 95% CI 0·20–0·98; p=0·044; I^2=0); however, the number of participants in this analysis was small (n=75).

We postulated that type of control care in our pre-specified subgroups might affect the overall effectiveness of self-monitoring. Yet, little difference was seen in terms of anticoagulation clinic care versus primary care for thromboembolic events (figure 3; χ^2 2·18, p=0·34); major

A	Self-monitoring	Control	O–E	Variance	HR (95% CI)	Interaction test
Sex						
Male	96/2453	124/2323	−17·57	54·73	0·40 (0·20–0·80)	
Female	18/539	28/555	−3·28	11·13	0·76 (0·36–1·58)	p=0·94
Age (years)						
<55	11/496	25/338	−9·17	8·37	0·33 (0·17–0·66)	
55–64	33/895	34/798	−2·17	16·59	0·80 (0·45–1·42)	
65–74	44/1038	66/1117	−9·88	27·06	0·69 (0·48–1·01)	
≥75	26/488	27/538	1·02	13·03	0·96 (0·41–2·26)	p=0·052
Indication						
Mechanical valve	36/1132	63/1040	−16·22	24·58	0·52 (0·35–0·77)	
Atrial fibrillation	70/1629	69/1623	−0·06	34·58	0·67 (0·28–1·57)	
Other	8/261	20/237	−3·87	6·30	0·54 (0·25–1·18)	p=0·032
Self-monitoring						
Self-testing only	89/1566	89/1557	−2·83	44·44	0·74 (0·30–1·82)	
Self-management	25/1487	63/1382	−18·52	21·57	0·42 (0·28–0·65)	p=0·002
Type of control group care						
Anticoagulation clinic	92/1959	112/1950	−11·46	50·83	0·44 (0·17–1·14)	
Primary care	16/995	27/893	−6·34	10·44	0·55 (0·28–1·08)	p=0·34
Total	**114/3053**	**152/2939**			**0·51 (0·31–0·85)**	

B						
Sex						
Male	201/2542	201/2403	−9·86	99·83	0·91 (0·74–1·10)	
Female	29/618	43/639	−5·15	17·56	0·75 (0·47–1·19)	p=0·45
Age (years)						
<55	25/500	24/340	−2·71	11·79	0·79 (0·45–1·41)	
55–64	66/812	44/699	6·67	27·16	1·28 (0·88–1·86)	
65–74	78/1110	101/1185	−11·66	43·86	0·77 (0·57–1·03)	
≥75	61/583	75/640	−4·48	33·49	0·87 (0·62–1·23)	p=0·20
Indication						
Mechanical valve	78/1111	91/1015	−10·11	41·66	0·78 (0·58–1·06)	
Atrial fibrillation	126/1676	119/1677	2·35	60·60	1·04 (0·81–1·34)	
Other	26/260	34/281	−6·90	13·87	0·61 (0·36–1·03)	p=0·13
Self-monitoring						
Self-testing only	190/1729	200/1719	−11·41	96·81	0·84 (0·64–1·12)	
Self-management	40/1487	44/1382	−3·27	20·89	0·86 (0·56–1·31)	p=0·87
Type of control group care						
Anticoagulation clinic	182/1959	187/1950	−8·27	91·58	0·91 (0·74–1·12)	
Primary care	42/1158	46/1055	−4·02	21·89	0·83 (0·50–1·36)	p=0·60
Total	**230/3216**	**244/3101**			**0·88 (0·74–1·06)**	

C						
Sex						
Male	204/2440	219/2297	−17·06	105·04	0·85 (0·70–1·03)	
Female	43/618	55/639	−2·81	24·11	0·89 (0·44–1·81)	p=0·84
Age (years)						
<55	14/495	15/353	−3·56	6·61	0·58 (0·22–1·57)	
55–64	46/874	46/781	−2·84	22·82	0·72 (0·36–1·41)	
65–74	98/1034	129/1112	−15·44	55·65	0·76 (0·58–0·99)	
≥75	89/583	84/640	4·74	42·91	1·12 (0·83–1·51)	p=0·19
Indication						
Mechanical valve	64/1101	75/1002	−9·66	34·54	0·80 (0·42–1·52)	
Atrial fibrillation	138/1555	156/1549	−14·32	72·67	0·72 (0·43–1·20)	
Other	45/334	43/349	3·71	21·53	1·19 (0·78–1·81)	p=0·23
Self-monitoring						
Self-testing only	195/1729	201/1719	−8·94	98·73	0·91 (0·75–1·11)	
Self-management	52/1342	73/1237	−12·04	31·05	0·75 (0·42–1·33)	p=0·15
Type of control group care						
Anticoagulation clinic	159/1934	173/1926	−10·62	82·83	0·82 (0·52–1·28)	
Primary care	72/988	90/884	−13·02	40·20	0·72 (0·44–1·18)	p=0·20
Total	**247/3071**	**274/2956**			**0·82 (0·62–1·09)**	

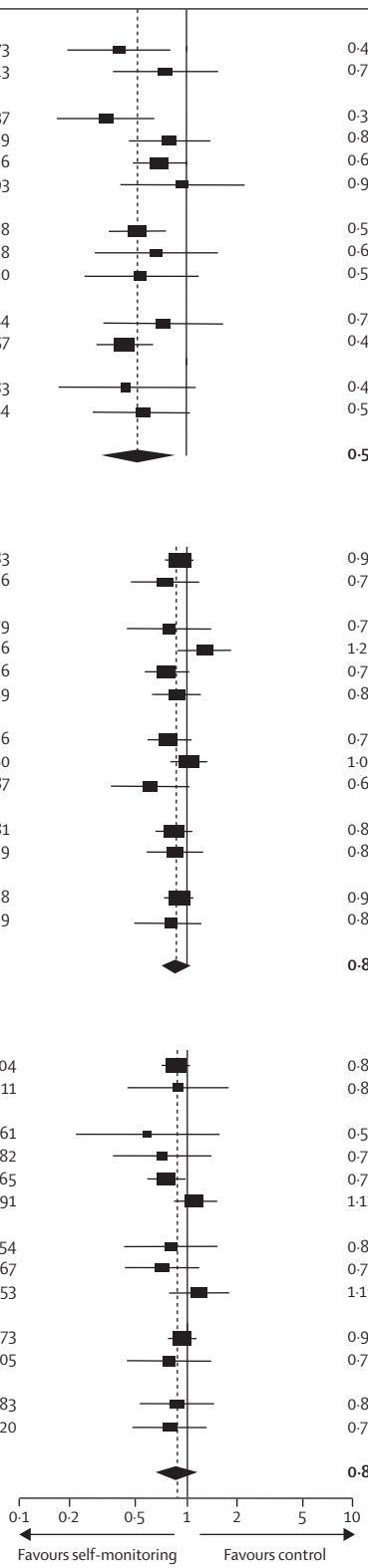

Figure 3: **Major outcomes by sex, age, indication, type of monitoring and control group care**
Thrombosis (A), major haemorrhage (B), and death (C). O–E=observed minus expected.

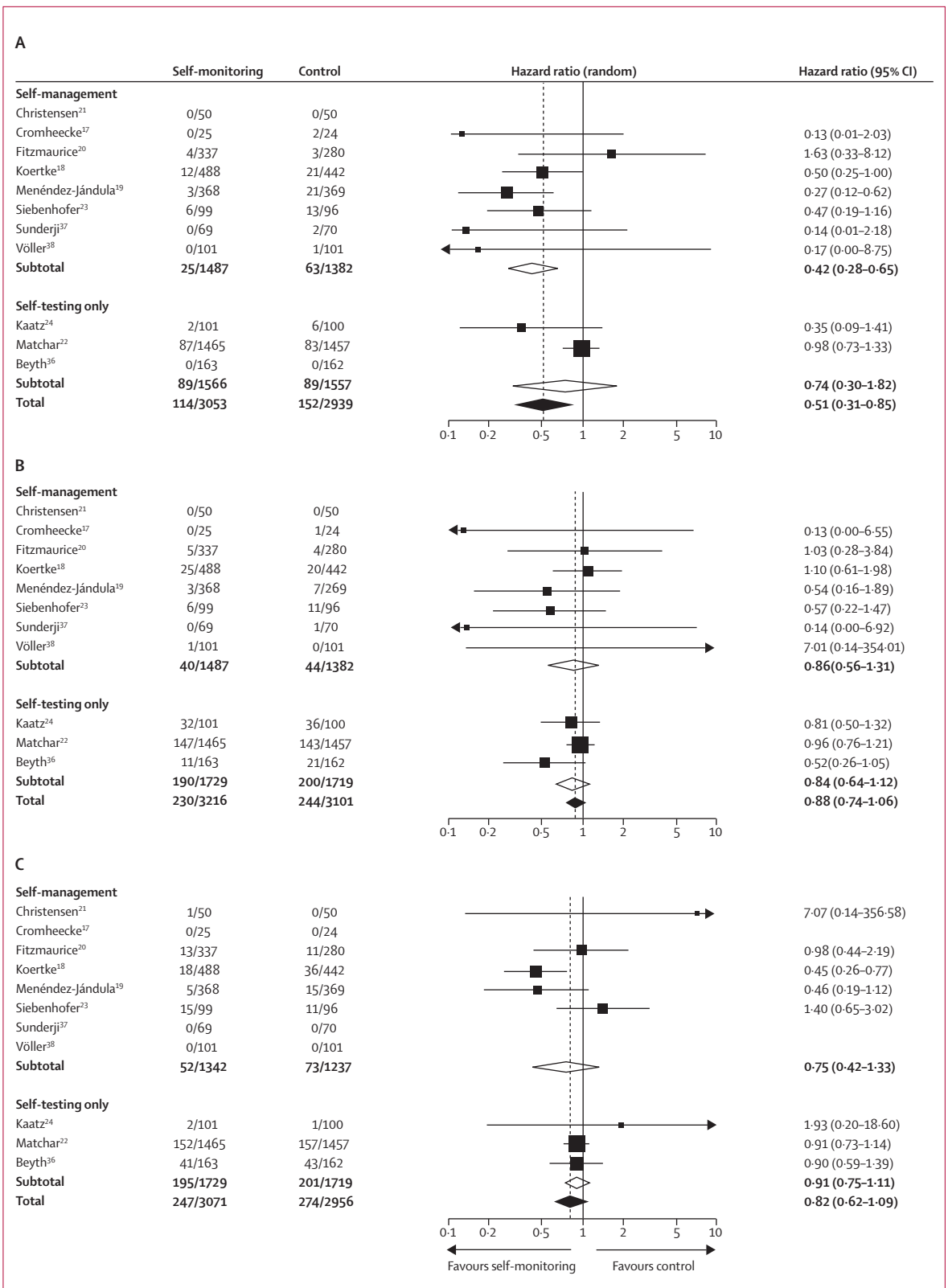

Figure 4: **Comparison by type of monitoring (self-monitoring compared with self-testing only)**
Thrombosis (A), major haemorrhage (B), and death (C).

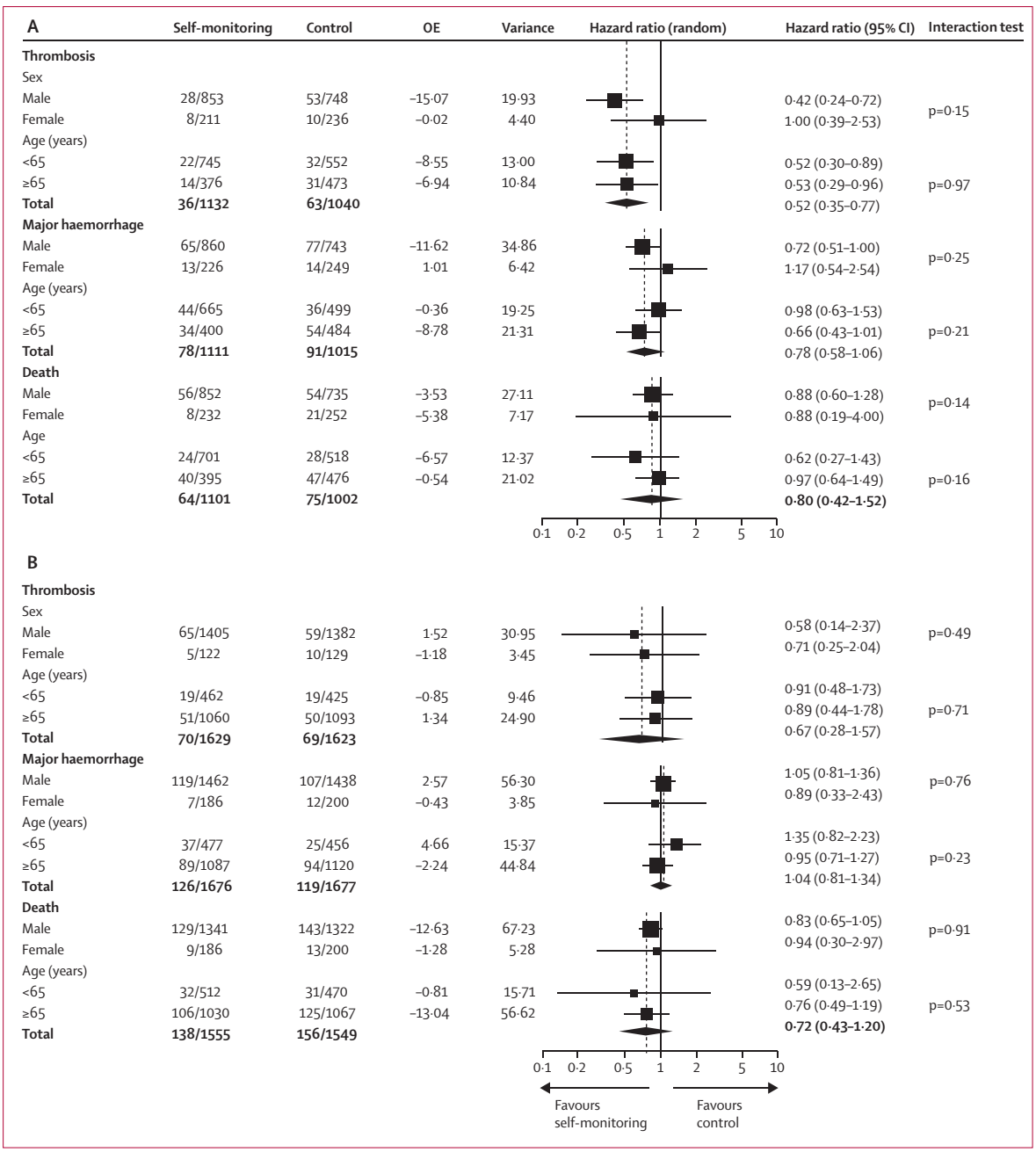

Figure 5: **Major outcomes in mechanical valve and atrial fibrillation by age and sex**
Patients with mechanical valve by sex and age (<65 years and ≥65 years; A) and patients with atrial fibrillation by sex and age (<65 years and ≥65 years; B). O–E=observed minus expected.

haemorrhage (χ^2 1·01, p=0·60), and death outcomes (χ^2 3·25, p=0·20).

A significant reduction in thromboembolic events was seen in men with a mechanical heart valve who were self-monitoring (figure 5; p=0·002, I^2=13·8), which was not significant in women (figure 5; p=0·99; I^2=5·8). However, the number of women was small (n=447 for thrombosis) and this interaction was not significant (χ^2 2·04, p=0·15). Men with a mechanical valve who were self-monitoring also had a significant reduction in major haemorrhagic events (figure 5; p=0·049; I^2=0), whereas women did not (figure 5; p=0·69; I^2=0). However, the interaction test was not significant (χ^2 1·31, p=0·25).

Participants younger than 65 years and those 65 years or older with a mechanical heart valve who were self-monitoring oral anticoagulation showed similar significant reductions with roughly a halving of thrombotic events (figure 5). We saw no significant

	Country	7 days		30 days		90 days		6 months		1 year	
		Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Cromheecke et al[17]	Holland	..	..	..	..	57·8 (14·5)	47·8 (18·6)	..	..	..	..
Körtke et al[18]	Germany	49·2% (42·9)	56·9% (41·3)	71·2% (28·7)	55·7% (35·5)	78·2% (22·0)	59·6% (32·5)	80·9% (20·0)	60·6% (31·2)	83·0% (18·6)	61·7 (30·8)
Menéndez-Jándula et al	Spain	66·7% (37·4)	62·5% (44·7)	66·2% (26·7)	68·2% (36·2)	66·2% (18·6)	68·5% (27·2)	68·0% (16·0)	69·0% (22·3)	67·9% (14·0)	68·8 (20·0)
Fitzmaurice et al[20]	UK	66·6% (40·4)	53·2% (45·3)	69·7% (32·2)	63·9% (36·8)	70·7% (25·1)	63·6% (31·7)	71·0% (23·0)	63·4% (28·8)	71·7% (22·0)	63·8 (28·4)
Christensen[21] et al	Denmark	80·2% (24·3)	61·7% (44·1)	78·3% (24·6)	71·2% (33·7)	77·5% (20·6)	67·7% (30·9)	75·5% (18·9)	67·3% (24·5)	75·5% (18·9)	67·4 (24·2)
Siebenhofer[23] et al	Austria	43·6% (43·5)	52·9% (44·0)	51·0% (36·6)	61·5% (35·8)	53·6% (26·2)	63·3% (29·7)	57·4% (24·5)	65·0% (26·5)	61·3% (19·9)	64·5 (21·1)
Matchar et al[22]	USA	63·3% (21·7)	52·3% (25·1)	63·5% (16·0)	53·0% (20·3)	64·1% (14·6)	55·1% (19·9)	65·1% (14·1)	57·7% (19·9)	67·2% (14·0)	61·0 (20·1)
Kaatz et al[24]	USA	59·7% (40·0)	61·1% (41·6)	56·6% (28·7)	66·9% (32·1)	62·9% (21·6)	70·0% (25·3)	64·7% (19·6)	71·6% (19·9)	65·9% (17·4)	70·8 (17·6)

Data are mean (SD).

Table 3: **Percentage mean time in therapeutic range at 7 days to 1 year**

	Time in therapeutic range			Number of tests		
	Mean difference between self-monitoring and control group (95% CI)	Heterogeneity	p value	Mean difference between self-monitoring and control group (95% CI)	Heterogeneity	p value
7 days	12·25% (8·99 to 15·51)	0	<0·001	0·25% (0·10 to 0·39)	77%	0·001
30 days	6·13% (–0·09 to 12·35)	72%	0·05	2·28% (1·59 to 2·97)	94%	<0·001
6 months	5·13% (–1·13 to 11·40)	79%	0·11	12·71% (9·33 to 16·10)	96%	<0·001
1 year	2·71% (–6·10 to 11·51)	94%	0·55	24·22% (18·40 to 30·04)	93%	<0·001

Data % or % (95% CI).

Table 4: **Mean difference between self-monitoring and control group in time in therapeutic range and number of tests for participants with a mechanical valve**

	Time in therapeutic range			Number of tests		
	Mean difference between self-monitoring and control group (95% CI)	Heterogeneity	p value	Mean difference between self-monitoring and control group (95% CI)	Heterogeneity	p value
7 days	10·38% (8·56 to 12·20)	0%	<0·001	0·01% (–0·25 to 0·28)	92%	0·91
30 days	3·16% (–4·07 to 10·39)	77%	0·39	1·78% (0·97 to 2·60)	97%	<0·001
6 months	4·40% (–0·86 to 9·67)	79%	0·10	12·03% (7·46 to 16·60)	99%	<0·001
1 year	5·13% (0·97 to 9·28)	57%	0·02	21·74% (13·11 to 30·37)	98%	<0·001

Data % or % (95% CI).

Table 5: **Mean difference between self-monitoring and control group in time in therapeutic range and number of tests for participants with atrial fibrillation**

effects or interaction in terms of major haemorrhage and death for other subgroups of participants with a mechanical valve. In participants with atrial fibrillation, we saw no significant effects across subgroups by sex or age, and no significant interactions (figure 5).

One study[17] provided data only at 90 days for the mean time in therapeutic range (table 3). The time in therapeutic range improved and SDs decreased over time. By 1 year, four trials[18,20–22] showed improvements in the intervention group, whereas the three trials,[19,23,24] which did not show improvement, all had smaller SDs in the intervention group. In the first 7 days participants with atrial fibrillation and a mechanical heart valve who self-monitored oral coagulation spent significantly more time in therapeutic range than did those who did not self-monitor (table 4, table 5), but over time the differences between groups reduced. Self-monitoring also led to an increase in the number of tests undertaken. At 1 year, participants with a mechanical valve or atrial fibrillation undertook more tests per year than did those receiving usual care (table 4, table 5). The substantial variation between studies was illustrated by the high heterogeneity.

Discussion

Our study used individual patient data for assessment of self-monitoring for oral anticoagulation. Overall, we

observed a significant reduction in thromboembolic events in the self-monitoring group. However, we did not find any significant effects for major haemorrhage or mortality.

Our findings accord with those of previous systematic reviews, in which patients who self-monitor or self-manage could improve the quality of their oral-anticoagulation therapy. However, despite the decrease in the number of thromboembolic events without concomitant increases in harms, we did not see the reduction in mortality shown in previous systematic reviews.[4–6] The odds ratio in a meta-analysis by Bloomfield and colleagues[39] was similar to our result for reduction in thromboembolic events (odds ratio 0·58, 95% CI 0·45–0·75; p<0·001). However, the result for death was similar in effect size, but the observed result differed significantly (odds ratio 0·74, 95% CI 0·63–0·87; p<0·001). This effect was highly heterogeneous (I^2=51%), which was attributed to the largest study to date.[22] Reasons given for this high heterogeneity were that this large study had substantially longer follow-up and higher quality of control in the usual care group than did other similar studies. The trend for reduction in mortality favoured self-monitoring, yet our previous estimate for a reliable and conclusive treatment effect would require 5150 participants in each study group.[6] Potentially, unavailable data from the ten studies that we were unable to access, were sufficient to remove the significance of this result.

Additionally, our previous estimate that self-monitoring was feasible for only half of patients requiring anticoagulant therapy might underestimate the true numbers. In the largest trial,[22] about 80% (2922 of 3643) of trained patients were competent in the use of self-monitoring equipment. Yet, even this estimate is confounded by eligibility criteria: in several trials[20,32] fewer than 50% of the potentially eligible patients were randomly assigned. Self-monitoring patients deemed not competent had higher numbers of practice attempts and higher cuvette wastage, and were less able to efficiently do a fingerstick procedure.[40] Factors associated with unsuccessful self-monitoring include refusal by patients, exclusion by their family practitioner, failure to pass training, old age, poor cognition, and poor manual dexterity.[6,20,40] One trial excluded people unable to attend training,[19] and in another trial[20] of an unselected population, young patients were more likely to successfully self-monitor oral anticoagulatoin.

In Germany 20% (160 000) of patients on anticoagulation undertook self-management, compared with only 1% of those in USA who did self-testing at home. Reasons for this difference include reimbursement, motivation by the patient, and willingness of the physician to support self-monitoring.[20] Limitations include the reluctance of individuals to participate, but also the direct costs to patients and the training required for effective monitoring.

In patients younger than 55 years of age, two-thirds reduction in thromboembolic events translated into 21 participants self-monitoring for 1 year to prevent one thromboembolic event. For patients with a mechanical heart valve, a 50% decrease in thromboembolic events meant that the number needed to undertake self-monitoring to prevent one event was 55 after 1 year and 24 over 5 years. By comparison, 63 patients are needed to prevent one heart attack with daily statin therapy over 5 years.[41,42]

Patients who self-tested and adjusted their doses had significantly lower rates of thromboembolic events, which suggests that patients should be given the opportunity, and provided with training, to undertake self-management. However, self-management does not mean that patients are left to fend for themselves: for instance, in one trial participants had 24 h back-up available,[37] and good quality control measures are needed. The type of control care did not affect the overall effectiveness of self-monitoring. This finding is often contradictory to the evidence, which shows that patients from community practices have significantly worse anticoagulation control than do those from anticoagulation clinics. However, the same systematic review highlighted that patients recruited to clinical trials tended to spend more time in the therapeutic range than did those in the community.[43]

For participants with atrial fibrillation we reported no significant effects across subgroups by sex or age, and no significant interactions. Participants with atrial fibrillation were older than those with a mechanical heart valve, and in this age group, rates of events tended to be low. In a previous trial of 973 elderly patients in the community on anticoagulation, thromboembolic events were 1·4% a year.[44]

Mean time in therapeutic range tended to be better in the self-monitoring groups. Importantly, even when the time in therapeutic range showed worse control, the SDs were less, which suggests lower variation and therefore more stable control of oral anticoagulation than in the control care group.[45] Full analysis of this issue is beyond the scope of this report, but is an important issue in establishing optimum anticoagulation control.

We also reported a reduction in mortality in very elderly patients who self-monitored oral anticoagulation. This result, although potentially misleading owing to the small numbers and number of analyses, warrants further investigation. The evidence already supports the use of anticoagulation for elderly patients unless contra-indications apply or patients decide the benefits are not worth the inconvenience of such treatment.[44] Our review was restricted to adults, although increasing numbers of children receive warfarin. But self-monitoring could be a safe and effective management strategy for children and clinical studies are recommended.[46]

Some limitations are worth noting. First, we could have missed a study, especially because of non-publication. The results differ for publication bias because of variation

in the methods for calculating Begg's and Egger's tests. Yet, the results of both suggest a weak effect of publication bias due to effects of small studies. Second, we were unable to obtain data from ten studies, although this was a small proportion of the overall dataset, which reduced the overall sample size. However, we were able to receive data from the largest trial to date, which was recently published.[22] Third, some heterogeneity in outcomes was obsereved. Differences occurred in the populations (ie, the monitor and the intervention populations), which all add to the inherent variability. Fourth, only a small number of participants aged over 85 years were included, and further research in this age group is needed. Finally, we do not know why fewer women than men were included and whether this is because women are reluctant to participate in self-monitoring or the overall recruitment strategies target men. One reason could be that in the largest study,[22] which comprised nearly half of the data, only 1·7% of the included participants were women. Furthermore, the study was done in a Veterans Affairs population, which mainly includes men.

Adoption of self-monitoring will depend on findings from economic analyses, which in the past have produced conflicting results. In the UK, a review concluded "in general, patient self-management is unlikely to be more cost-effective than the current specialised anticoagulation clinics,"[47] whereas a Canadian study suggested: "self-management is a cost-effective strategy for patients receiving long-term oral anticoagulation therapy for atrial fibrillation or for a mechanical heart valve".[48]

We believe the results of our review will lead to a systematic change in practice, in terms of the significant reduction in thromboembolic events in patients with a mechanical heart valve requiring long-term anticoagulation. Such patients should be offered the option to self-manage their disease with suitable health-care support as back-up. Additionally, several reviews and our study show that self-monitoring and self-management is a safe option for suitable patients.[5,6,49]

Contributors

Members named in the writing committee contributed to the data collection or the systematic review and data analysis, and to the preparation of the published Article.

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Conflicts of interest

Department of Primary Health Care, Oxford University (UK) received funding from the National Institute for Health Research Technology Assessment Programme (NIHR HTA; UK) and NIHR National School for Primary Care Research (UK); Iberoamerican Cochrane Centre received funding from Instituto de Salud Carlos III; Jack Ansell received funding from Alere ITC; Rebecca Beyth received funding from the 5th International Patient/Physician Conference on Oral Anticoagulant Therapy and the NIHR, University of Florida, Department of Veterans Affairs, and US National Institutes of Health; Robert Edson received funding from VA Cooperative Studies Program; Alain P A Gadisseur received funding from Roche Diagnostics, Bayer Healthcare and Boehringer Ingelheim; Department of Haemotology, Antwerp University Hospital (Germany) received funding from Bayer Healthcare; University College London Hospital (UK) received funding from Roche Diagnostics; J Michael Hasenkam received funding from Roche Diagnostics, Johnson & Johnson, Edwards Lifesciences, and Nycomed; Department of Cardiothoracic Surgery, Aarhus University Hospital (Denmark) received funding from National Board of Health; Alan Jacobson received funding from Anticoagulation Forum, Loma Linda Veterans Association for Research, Biosite Corporation, Boehringer Ingelheim, Daiichi Sankyo, Farallon Medical, Hemosene, Inverness Medical, Pfizer Medical, Quality Assured Services, Roche Diagnostics, Sanofi-Aventis, Tapestry Medical, GlaxoSmithKline, and VA Cooperative Studies Program and was the co-chair of the THINRS study; Department of Internal Medicine, Loma Linda University (USA) received funding from Loma Linda Veterans Association for Research, Biosite Corporation, Boehringer Ingelheim, Farallon Medical, Hemosene, Inverness Medical, and Sanofi-Aventis; Scott Kaatz received funding from Biosite and Vox media; Department of Internal Medicine, Henry Ford Hospital (USA) received funding from Roche Diagnostics; Institute of Cellular Medicine, University of Newcastle (UK) received funding from Heart Research UK; Wolfson Unit of Clinical Pharmacology, School of Clinical and Laboratory Sciences, University of Newcastle (UK) received funding from the BUPA Foundation and Coaguchek; Anticoagulation Europe received funding from Roche Diagnostics; David Matchar received funding from Boerhinger Ingelheim, Roche, and VA Cooperative Studies Program and was the Co-Chair of the THINRS study; Juan Carlos Souto is the Scientific Director of Monitor Medical.

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