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

C Heneghan, P Alonso-Coello, J M Garcia-Alamino, R Perera, E Meats, P Glasziou

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-dosing) 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.13

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.14 Such handheld devices have proved sufficiently reliable.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-dosing) 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. 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 Mantel-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 χ² and I² statistics. 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). 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). Trials were from the UK (4),
### Table 1: Study characteristics

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Duration of study (months)</th>
<th>Mean age (years)</th>
<th>Numbers analysed</th>
<th>Control-group intervention</th>
<th>Education and intervention for self-monitoring group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honthotto 1998, Germany[39]</td>
<td>N/A</td>
<td>N/A</td>
<td>75</td>
<td>75</td>
<td>Managed by home physician. Standardised training. Measured INR twice a week, and contacted coagulation clinic by phone.</td>
</tr>
<tr>
<td>Beyth 2000, USA[42]</td>
<td>6</td>
<td>75</td>
<td>162</td>
<td>163</td>
<td>Managed by primary care physician as per usual practice. 1-h education session, patients phoned results to coach who made recommendations. Two educational sessions, self-adjusted.</td>
</tr>
<tr>
<td>Cromheecke 2000, Netherlands[43]</td>
<td>3</td>
<td>42</td>
<td>49</td>
<td>49</td>
<td>Testing at intervals of 1-2 weeks and managed by a specialised anticoagulation service. Two educational sessions, self-adjusted.</td>
</tr>
<tr>
<td>Kortle 2001, Germany[44]</td>
<td>24</td>
<td>62.5</td>
<td>295</td>
<td>305</td>
<td>Managed by primary care physician as per usual practice. Trained in self-monitoring. 6-11 days after operation.</td>
</tr>
<tr>
<td>Sidhu 2001, UK[45]</td>
<td>24</td>
<td>61</td>
<td>48</td>
<td>34</td>
<td>Managed by family doctor as per usual practice. Two educational sessions, doctor availability to receive calls, patients self-adjusted as per protocol.</td>
</tr>
<tr>
<td>Khan 2004, UK[47]</td>
<td>6</td>
<td>Median 73</td>
<td>39</td>
<td>40</td>
<td>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.</td>
</tr>
<tr>
<td>Sundérg 2004, Canada[48]</td>
<td>8</td>
<td>60</td>
<td>70</td>
<td>69</td>
<td>Managed by primary care physician as per usual practice. Two educational sessions, self-adjusted using a nomogram.</td>
</tr>
<tr>
<td>Voller 2005, Germany[50]</td>
<td>5</td>
<td>64</td>
<td>101</td>
<td>101</td>
<td>Managed by family doctor as per usual practice. Standard training course of three sessions.</td>
</tr>
</tbody>
</table>

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

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. Two trials included patients on long-term anticoagulation for atrial fibrillation: one of these provided no reported outcomes in the control group. Nine trials included patients on long-term anticoagulation for any indication. In seven trials the intervention groups adjusted therapy themselves; five trials used non-adjusted therapy. One further trial reported information on adjusted (Gadisseur a) and non-adjusted therapy groups (Gadisseur b; table 1). Eight trials used primary care for the control group and six studies used specialist anticoagulation clinics. Duration of studies varied from 2 months to 24 months. Four trials were judged to be of poor quality 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: 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, the effect was larger than in those in which patients self-monitored only: this subgroup interaction was not significant (p=0.12). In three trials
in which patients had mechanical valves26,28,31 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,25,26,28,29 there was a significant reduction in events. The 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:21,23,25,27,28–34 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
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.24,25 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.21,29

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, I²=64%). One trial29 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-
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.

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

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

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Self-management n/N</th>
<th>Control n/N</th>
<th>OR (Fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Self-adjust*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sawicki 1999</td>
<td>1/83</td>
<td>1/82</td>
<td>2.26</td>
<td>67.8</td>
<td>0.99 (0.06–16.06)</td>
</tr>
<tr>
<td>Sidhu 2001</td>
<td>0/34</td>
<td>4/48</td>
<td>8.39</td>
<td>47.1</td>
<td>0.14 (0.01–2.75)</td>
</tr>
<tr>
<td>Fitzmaurice 2002</td>
<td>0/23</td>
<td>1/26</td>
<td>3.14</td>
<td>33.4</td>
<td>0.36 (0.01–9.32)</td>
</tr>
<tr>
<td>Sunderji 2004</td>
<td>0/69</td>
<td>0/70</td>
<td>Not estimable</td>
<td>0.39</td>
<td>0.38 (0.15–1.02)</td>
</tr>
<tr>
<td>Menendez-Jandula 05</td>
<td>6/368</td>
<td>15/369</td>
<td>33.45</td>
<td>47.2</td>
<td>0.37 (0.16–0.95)</td>
</tr>
<tr>
<td>Voller 2005</td>
<td>0/101</td>
<td>0/101</td>
<td>Not estimable</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>6/70</td>
<td>696</td>
<td></td>
<td>100.0</td>
<td>0.61 (0.38–0.98)</td>
</tr>
<tr>
<td>02 Non-adjust†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White 1989</td>
<td>0/25</td>
<td>0/24</td>
<td>Not estimable</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Bayth 2000</td>
<td>21/163</td>
<td>26/162</td>
<td>1.18</td>
<td>51.5</td>
<td>0.77 (0.47–1.44)</td>
</tr>
<tr>
<td>Kortke 2001</td>
<td>0/295</td>
<td>0/292</td>
<td>Not estimable</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Gardner 2004</td>
<td>5/23</td>
<td>5/25</td>
<td>Not estimable</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>52/23</td>
<td>52/25</td>
<td></td>
<td>100.0</td>
<td>0.81 (0.44–1.49)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1201</td>
<td>1201</td>
<td></td>
<td>100.0</td>
<td>0.61 (0.38–0.98)</td>
</tr>
</tbody>
</table>
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.41 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 Glassziou analysed and interpreted data. C Heneghan, R Perera, J M Garcia-Alamino, P Alonso-Coello, and P Glassziou drafted the manuscript. Statistical analysis was done by R Perera, C Heneghan, and P Glassziou.

Conflict of interest statement
We declare that we have no conflict of interest.

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Role of the funding source
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References


